EXHIBIT 22

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF VERMONT

CASE NO. 5:16-cv-125

SULLIVAN, ET AL. V. SAINT-GOBAIN PERFORMANCE PLASTICS CORP.

REBUTTAL REPORT OF PHILIPPE GRANDJEAN, MD, DMSc

PREPARED AND SUBMITTED ON BEHALF OF PLAINTIFFS

1 August, 2018

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I. INTRODUCTION

My name is Philippe Grandjean. I have been asked by counsel for plaintiffs to provide, from a medical and epidemiological perspective, an expert rebuttal report responding to certain opinions offered by three experts retained by defendant Saint-Gobain. Specifically, I have been asked to provide an evaluation of the human health risks associated with environmental PFOA contamination from Saint-Gobain's manufacturing and disposal operations in North Bennington and Bennington (Bennington), VT. As PFOA, as well as related PFASs,[a] are proven hazardous substances, elevated PFOA exposure from releases from the Saint-Gobain facilities in Bennington results in an increased risk of contracting serious disease that can be identified in early, latent stages by using existing diagnostic procedures. This rebuttal report is based on my education and experience as a physician and environmental epidemiologist, my own PFAS research, and on my review of the scientific literature and regulatory standards for those chemicals, as outlined below.

A. Qualifications

I earned my M.D. and D.M.Sc. degrees from the University of Copenhagen, Denmark, in 1974 and 1978, respectively.

I serve as Adjunct Professor of Environmental Health at the Harvard School of Public Health (since 2003) and as Professor and Chair of Environmental Medicine at the University of Southern Denmark (since 1982). I previously served for a brief period (1980-1982) as the Director of the Department of Occupational Medicine at the Danish National Institute of Occupational Health. Former positions in the U.S. include Research Fellow and Senior Fulbright Scholar, Mount Sinai School of Medicine in New York (1978-1979), and Adjunct Professor of Neurology and Environmental Health, Boston University Schools of Medicine and Public Health (1994-2002). As part of my employment as a civil servant in Denmark, I have served for more than 30 years as the Consultant in Toxicology to the Danish Health Authority. In the latter capacity, I have reviewed and commented on case reports, research studies, and proposed regulations on environmental chemicals. I also serve on the Scientific Committee of the European Environment Agency (EEA).

The main focus of my research in environmental epidemiology focuses on the health effects of exposures to environmental chemicals, with the main emphasis on perfluorinated alkylate substances (PFASs).[a] Most of my efforts have concentrated on the effects of environmental pollutants on early human development. My research has been entirely funded by public sources, mainly the National Institutes of Health. My current funding includes an $8 million center grant from the Superfund Research Program (National Institute of Environmental Health Sciences), where I serve as the co-lead and PI for one of the four center projects. The

[a] Terminology concerning perfluorinated compounds has evolved. The term PFC had been used to refer generally to perfluorinated compounds. Recently, the scientific community has with more precision started to settle on the term PFAS to refer to the narrower family of perfluorinated alkylate substances, which family includes PFOA (and PFOS), and essentially all releated chemicals relevant in this matter. For ease of reference, and for consistency, I will, for the most part, use the term PFASs to refer to the group of perfluorinated compounds concerned in the present case, and will use more specific terms as appropriate. A table of the abbreviations I use in this report is attached as Exhibit A.

Center focuses entirely on PFASs, how they disseminate, biomagnify and cause adverse health effects. I recently received support from the Danish Research Council for an international multi-center study on weight gain after dieting and the effects of PFAS exposure.

I have published about 500 scientific papers, of which most are research articles in international scientific journals with peer review. My h-index in the Web of Science data base is 64, and my work is cited well over a thousand times every year. Seven of my articles published in the last 10 years have earned the attribute "Highly Cited Paper," i.e., they received enough citations to place them in the top 1% of published papers in the field. This list includes an article on PFAS immunotoxicity published in the Journal of the American Medical Association (JAMA) in 2012. I have also authored or edited 20 books, including textbooks on environmental health and risk assessment.

I am regularly invited as speaker at international conferences and other scientific events. Regarding PFASs, I was invited in 2012 to give a special presentation at the meeting of the (U.S.) National Advisory Environmental Health Sciences Council (at the National Institute of Environmental Health Sciences) and also at a meeting of the Emerging Chemicals Workgroup, U.S. Environmental Protection Agency (EPA). Both presentations were on the immunotoxicity of PFASs. In the fall of 2016, I was invited to give a special presentation on PFOA at the committee meeting of the United Nations Stockholm Convention. In June this year, I presented on health risks from PFAS exposure at a meeting of the Society for Risk Analysis. Among my speaking commitments later this year is a special seminar on PFASs to be held at the Agency for Toxic Substances and Disease Registry (ATSDR).

I am (Founding) Editor-in-Chief of the open-access scientific journal, Environmental Health (since 2002), which ranks among the upper 25% of journals in the field. I also serve or have served on editorial boards of about a dozen journals within medicine, environmental science, and toxicology. As editor and as reviewer for other major journals, I frequently evaluate manuscripts on environmental epidemiology and toxicology.

I have served on, sometimes chaired, or acted as rapporteur for, expert committees under the auspices of the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), EPA, the European Commission, the European Food Safety Authority (EFSA), and other organizations. During my six-year membership of an EFSA expert panel, I participated in developing the opinion on 'Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts' [1] and the 'Guidance of the Scientific Committee on Use of the benchmark dose (BMD) approach in risk assessment' [2].

I recently served as a health expert for the State of Minnesota in a law suit against the 3M Company (State of Minnesota District Court for the County of Hennepin, Fourth Judicial District, Civil Action No. 27-CV-10-28862).

A copy of my most recent CV is attached as Exhibit B. A list of publications which I authored or co-authored, including those of the past 10 years, is attached as Exhibit C.

B. Materials relied upon

For the purposes of this rebuttal report, I have relied in part on my own epidemiological research and publications concerning PFASs. I also have reviewed the epidemiological literature concerning studies by others on the human health risks associated with exposure to PFASs. The endnote references are listed in Exhibit D. Among other sources of information, such as the reports from the C8 panel [3], I have relied upon the most recent version of ATSDR's draft ToxProfile [4], also the latest update [5], the evaluation of immunotoxicity by the National Toxicology Program (NTP) [6], the assessment of carcinogenicity by IARC [7], and other recent reviews [8-11].

In addition to epidemiological studies, I have considered certain supporting toxicological information from laboratory animal studies and *in vitro* models, but I do not necessarily provide a complete review of all such supporting evidence, as my focus is human health. I emphasize the methodology of evaluating the strength of the evidence, and I outline the emergence over time of the knowledge on human PFAS exposures and associated risks. My focus is on adverse health outcomes where medical monitoring is likely to provide a benefit to exposed individuals.

I have benefitted from access to and review of Dr. Alan Ducatman's two expert reports previously submitted in this case, as well as his expert rebuttal report. I have also reviewed the reports of the three experts retained by Saint-Gobain to respond to Dr. Ducatman – Professor Edward J. Calabrese, PhD, Professor Philip S. Guzelian, MD, and Professor Jeffrey H. Mandel, MD, MPH (defense experts). Additionally, I have reviewed the following materials: Third Amended Complaint [Doc. 113]; Order on Motion to Compel Production of Medical Records [Doc. 105]; VT Dept. of Health Sept. 2017 PFOA Blood Testing and Exposure Assessment; VT Dept. of Health June 22, 2016 PFOA/PFOS Drinking Water Advisory; VT Dept. of Health July 10, 2018 Drinking Water Advisory for Five PFAS Substances; VT Agency of Natural Resources Map of Zone of Contamination; North Bennington and Bennington Private Well Test Results, Updated Sept. 2017; Merits Expert Report of Don Siegel dated 12.15.17; and May 2, 2018 Supplemental Expert Report of Donald R. Brandt.

C. Exhibits

I may use as exhibits part or all of any of the documents or papers cited in this report including this report itself; graphs or tables drawn from data in any of those documents or papers; any document helpful as foundation for or illustration of my testimony.

D. Updates and reservation

The opinions expressed in this rebuttal report are my own and are based on the data, documents, and facts available to me at the time of writing. Should additional relevant or pertinent information become available, I reserve the right to supplement the discussion and findings in my report. I also reserve the right to respond to any opinions on similar topics by other experts in this matter, and to respond to any criticism or comment on my opinions.

E. Compensation

I am being compensated at the rate of $250 per hour for my time, which is my customary rate for matters of this type. My compensation does not depend in any way on the content of my opinions.

F. Previous service as expert at deposition or trial during last 4 years

State of Minnesota District Court for the County of Hennepin, Fourth Judicial District, Civil Action No. 27-CV-10-28862), deposition only.

United States District Court for the Eastern District of Missouri (United States of America, et al. v. Ameren Missouri, Case No 4:11Cv77), deposition only.

II. SUMMARY OF REBUTTAL OPINIONS

The major opinions expressed in this rebuttal report, which are discussed below in more detail along with more minor and supportive opinions, can be generally summarized as follows:

- Contrary to the contentions of defense experts, elevated human exposure to PFASs pose a substantial present and potential hazard to human health. In particular, it is my opinion, based on the weight of the epidemiological evidence and supporting toxicity evidence, that exposure to PFOA results in an increased risk of harm to at least human
    - immune system functions,
    - reproductive functions including adverse effects to the next generation,
    - endocrine functions, including increased risk to thyroid disease and diabetes,
    - liver function,
    - and by increasing the risk of cardiovascular disease and certain types of cancers.

- PFOA exposure within ranges of so-called background levels shows convincing associations with several adverse outcomes, most of which may be detected at latent stages early in the disease process, thus facilitating beneficial treatment.

- Contrary to the contentions of defense experts, adverse health effects have been documented in epidemiological studies within ranges of background exposures similar or even below the elevated, above-background exposures occurring in the Bennington, VT "Zone of Contamination" in and around the Saint-Gobain facilities. These exposures are therefore, as concluded by Dr. Ducatman, associated with increased risks of disease development.

- Because independent PFAS research began only recently, our understanding of PFOA toxicity has developed substantially only in recent years. By now, risks to human health have been identified at exposure levels that in the past were considered safe, and ongoing research will likely show additional risks at background exposures. The defense experts opine that the evidence available does not satisfy their own and very strict "criteria" for

causality, but these criteria are not in accordance with weight-of-evidence procedures applied by regulatory agencies and international organizations.

- I conclude that members of the "Exposure Class" of residents, as a result of their above-background exposures to PFOA through ingestion of drinking water substantially contaminated with PFOA, have been exposed to a proven hazardous substance and therefore suffer from an increased risk of developing serious disease. I concur with Dr. Ducatman's opinion that a medical monitoring program is appropriate and will be useful for the early detection of early, potentially treatable stages of disease through current clinical methods, and that the significantly increased risk makes medical monitoring necessary beyond what would regularly be prescribed in the absence of exposure.

III. BACKGROUND ON PFAS PRODUCTION AND CONTAMINATION

A. A short history of PFAS production in Bennington, VT

By way of brief background, my understanding of the history of PFAS production is basically as follows.[b]

Saint-Gobain Performance Plastics Corp. operated manufacturing facilities in Bennington and North Bennington, VT, and utilized PFOA in these manufacturing operations.[c] The PFOA was fused to fiberglass fabric at high temperatures in coating towers, but over the years the company either did not use any emission control systems, or used ineffective systems, to reduce or eliminate PFOA emissions into the surrounding Bennington community.

The exposure situation in Bennington, VT, resembles PFAS contamination problems elsewhere in the U.S., including other New England sites owned by Saint-Gobain.

B. Widespread, persistent environmental contamination

By way of background, I shall outline my basic understanding of environmental PFAS contamination.

Major physicochemical properties of PFASs were characterized in publications as early as 1951 [12]. Standard chemical handbooks listed PFAS vapor pressures and water solubilities at least by the 1970s (although they may not have been accurate). Many PFASs (or their salts or precursors) are somewhat water soluble and can potentially leach through soil to reach the groundwater, while some compounds have a sufficient vapor pressure to allow their dissemination via the atmosphere. These properties must have been known at PFAS-producing or using industries in the 1970s or earlier than that.

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[b] I mainly rely on the Third Amended Complaint [Doc. 113].

[c] Saint-Gobain first began operations on Northside Drive in Bennington in 1968, and moved its manufacturing operations to 1030 Water Street in North Bennington in 1978, where it operated until approximately 2002. Future reference to the "Saint-Gobain facility" refers to the former Saint-Gobain manufacturing facility located at 1030 Water Street in North Bennington, VT.

PFASs do not occur naturally. Many PFASs show high thermal, chemical and apparent biological inertness, properties that made them useful for certain industrial purposes, though at the same time also rendering these compounds an environmental hazard due to the potential for persistence and bioaccumulation [13]. The carbon-fluorine bond is strong, thus making the PFASs virtually indestructible in the environment and in the human body. However, as an industry-supported report claimed in late 1997, organofluorine compounds are "generally viewed as recalcitrant because of their lack of chemical reactivity" [14].

Although most PFASs are oleophobic and therefore do not accumulate in fatty tissues (in contrast to dioxin, polychlorinated biphenyls [PCB], and other persistent compounds); especially PFOS is now known to bioaccumulate in aquatic and marine food chains [14]. Long-range aqueous transport allows PFASs in their soluble anionic forms to reach remote locations. In addition, several precursor compounds can be metabolized to PFOA and PFOS in the environment or in humans. The global dissemination of PFASs also occurs through atmospheric transport of volatile precursors, which are metabolized into the more persistent PFASs that are then deposited. Pollution of terrestrial and aquatic food chains resulted in high concentrations of PFOS in vulnerable species even in remote ecosystems, including, for example, polar bears [15, 16].

The Stockholm Convention was launched by the United Nations in 2001 and first included "the dirty dozen". Appendix B (substances to be restricted) now includes PFOS, and PFOA is currently under final review before a decision on inclusion, most likely in Appendix B. As discussed in Section IX, ECHA has already listed PFOA on the EU Candidate List of substances of very high concern (SVHCs), for which mandatory authorization procedures apply. These agencies regard PFOA a human health hazard.

C. Environmental contamination in Southwestern Vermont[d]

I understand that the manufacturing operations at the Saint-Gobain facility involved the treatment of fiberglass products with PFOA and that the operations resulted in substantial releases of PFOA to the environment. As outlined in Dr. Alan Ducatman's reports, the exposure situation can be summarized in part as follows:

- For an unknown period – possibly beginning decades ago – residents in the Bennington, VT, Zone of Contamination have consumed drinking water contaminated with elevated levels of PFOA. The total number of residents exposed to this pollution over time is likely to be approximately one thousand.[e]

- A blood testing program conducted by the State of Vermont of local residents showed that serum concentrations of PFOA in many residents greatly exceeded national levels and that the degree of water contamination and water consumption were associated with elevated serum-PFOA concentrations in local residents.[f]

[d] Map showing the Zone of Contamination.
[e] Supplemental Expert Report of Donald R. Brandt (May 2, 2018).
[f] Vermont Department of Health. Exposure to Perfluorooctanoic Acid (PFOA) in Bennington and North Bennington, Vermont: Results of Blood Testing and Exposure Assessment, September 2017.

- Serum-PFOA concentrations are known to decrease only slowly. However, the cumulated PFOA burdens in past and present exposed Bennington residents will remain elevated for many years to come and will depend on the extent to which any continued exposures are minimized.

- The small study carried out by the State in Bennington demonstrated that some of the suspected adverse health outcomes were indeed associated with elevated serum-PFOA concentrations.

PFOA concentrations are generally reported in terms of weight. One µg (microgram) is one millionth of a gram, and this unit is one thousand times greater than 1 ng (nanogram), which is one billionth of a gram. Sometimes, concentrations of PFOA in water are expressed in terms of parts per trillion (ppt), which refers to the relative weight of the contaminant. One ppt is therefore the same as 1 ng/L, or 0.001 µg/L. Such concentrations may seem miniscule, but when contaminated water is consumed, the PFOA is retained in the body, while the water is eliminated via urine, sweat, and exhaled air. In regard to adverse health risks, the key parameter is therefore the total amount of PFOA ingested, not the ppt concentration as such.

The State of Vermont has adopted a 20 ng/L guideline for PFOA (and PFOS) as a legal standard for groundwater quality.[g] This limit was tightened in July, 2018 to represent the sum of five PFASs, now also including PFHxS (perfluorohexane sulfonic acid), PFHpA (perfluoroheptanoic acid), and PFNA (perfluorononanoic acid).[h]

Some currently recommended guidelines are higher, but they have greatly decreased with time and are expected to further decrease, as reviewed in Section IX.

It is not known precisely when the groundwater contamination in Bennington, VT, began. Releases from the Northside Drive facility stacks commenced in 1968, and first caused soil pollution. Due to the persistence of PFOA and its solubility in water, the soil contamination led to ground water pollution, and a plume developed and then contributed to contamination of private wells starting decades ago.[i]

As PFASs are not removed from drinking water by standard treatment processes, granular activated carbon system must be installed. Depending on the location, this may be required both for community water supply systems and for private wells. Although quite efficient and capable of reducing contaminant levels below the current EPA and Vermont guidelines, such treatment may not necessarily provide sufficient protection as needed to maintain levels below those that are associated with adverse health effects.

Evidence has accumulated that PFOA and other PFASs are excreted in human milk [17]. Analyses of paired samples of maternal serum, cord serum, and maternal milk have demonstrated that PFASs are transferred through the human placenta and via human milk [18,

[g] Vermont Health Advisory Rationale - PFOA/PFOS Health Advisory dated 06/22/2016.
[h] Vermont Department of Health, http://www.healthvermont.gov/sites/default/files/documents/pdf/ENV_DW_PFAS_HealthAdvisory.pdf
[i] Merits Expert Report of Don Siegel dated 12.15.17

19]. During breast-feeding, the cumulated postnatal exposure to PFASs through lactation can be substantial, especially for PFOA [19], thereby causing additional exposures during sensitive early development. From serial blood samples in young children, a recent study showed that breastfeeding could increase an infant's blood concentrations of PFASs to several-fold above the mother's [20]. Thus, the PFOA contamination from the Saint-Gobain facility has disproportionally affected children born to mothers exposed to PFOA emitted from the plant(s).

Additional to PFASs in maternal milk, infants fed formula prepared with contaminated drinking water have been substantially exposed to PFASs. Observed ratios between PFOA concentrations in drinking water and human serum and between concentrations in human serum and milk suggest that milk concentrations may approximate those occurring in contaminated drinking water [8]. Thus, infants from the contaminated communities likely had highly elevated exposures no matter they were breastfed or bottle-fed. A contributing factor is that infants and children have a higher fluid consumption compared to adults on a body weight (bw) basis.

I note that the accumulated evidence on exposure via breastmilk as well as transplacental passage has inspired downward revisions of the guidelines for PFOA and PFOS in drinking water at the state level [21]. These findings suggest that risk assessments relying on life-time exposures underestimate the true risks to the exposed population, as the fetus and the infant are undergoing rapid development that render them highly susceptible to PFAS toxicity, as further discussed in Section VIII.

In conclusion, it is likely that approximately one thousand residents have been exposed to PFOA from environmental pollution from the Saint-Gobain facility which has contaminated hundreds of drinking water wells in the Bennington Zone of Contamination.[j] This PFOA contamination may have reached the residents' wells many years ago, perhaps as much as 40 years ago.[k] Because the PFASs are transferred via the placenta and excreted in human milk, the next generation must be considered at particular risk, whether breastfed or bottle-fed with substitute made with contaminated water.

IV. HUMAN EXPOSURE TO PERFLUORINATED COMPOUNDS

A. Detection and distribution of PFASs in humans

The long-chain PFASs are persistent in the human body and therefore stay in the blood and in organs for a long time. They may be excreted in urine, though only slowly, and the elimination half-lives are several years. This means that a continuing exposure results in accumulation of the PFASs in the body. The concentration in a blood sample therefore reflects exposures that happened during the past several years. On the other hand, when exposure stops, then elimination will be slow, usually with a constant fraction being excreted each month, each year. First-order toxicokinetics are usually assumed, i.e., that constant fractions of serum

[j] North Bennington and Bennington Private Well Test Results, Updated Sept. 2017.
[k] Merits Expert Report of Donald I. Siegel, December 15, 2017, at pp. 3-4.

concentrations are eliminated over time [22, 23]. The time it takes for half the compound to be eliminated is called the (biological or elimination) half-life.

From serial analyses of serum samples from former 3M production workers after retirement, half-lives for long-chain PFASs have been estimated to be ~3years (PFOA), ~5years (PFOS), while most short-chain PFASs have a relatively short T½ in serum [24]. However, the serum half-life for PFHxS is even longer, i.e., ~9 years. If the exposure is not completely eliminated during the follow-up, the body burden will decrease more slowly (if at all). Taking this concern into account, the elimination half-life for PFOA is approximately 3 years [25].

Still, calculations based on serum concentrations may be erroneous, as very high PFAS concentrations in various organs show that "deep" compartments, e.g., in the liver, may have much longer retention times [26]. Although toxicokinetic modeling may also depend on the range of blood concentrations and the individual variability associated with model parameters [23], reasonable results have been obtained modeling PFOA kinetics using a first-order model [22, 27]. This approach has been used by the C8 Panel to estimate serum concentrations both before and after blood sampling. EFSA [28] considers Loccisano's model [29] the most appropriate for linking daily intake to blood concentrations.

Because major PFASs, such as PFOA, have elimination half-lives of several years, a serum concentration measured at a certain point in time represents not only the concurrent accumulation, but also serum levels in the past. If exposures have been regular, the serum-PFOA may represent a long-term exposure. The stability of the PFASs has implications for the interpretation of epidemiology studies. Thus, cross-sectional studies are much more meaningful and carry greater weight for substances like PFOA that remain in the body for several years.

Laboratory animals, especially the rat, show different retention patterns and even sex-related differences in elimination rates. Most laboratory animals have much shorter elimination half-lives than humans. In interpreting toxicology studies, the specific accumulation patterns must therefore be considered, and proper interspecies comparisons may rely on serum concentrations (or tissue concentrations), rather than dose levels.

B. Serum analyses from Bennington, VT, residents

PFOA is a long-chain PFAS that is very stable in the body and therefore has a long half-life in serum. PFOA therefore accumulates and remains in the body up to many years after cessation of the exposure. As residents in the Zone of Contamination for an unknown period, that likely lasted decades, have consumed drinking water contaminated with PFOA, body burdens and serum concentrations of PFOA in long-term residents likely represent accumulations over several decades.

The Vermont Department of Health carried out a study of PFOA concentrations in the blood of Bennington residents and found that they are strongly correlated with PFOA levels in well water, i.e., that consumption of contaminated drinking water was the primary

source of exposure to PFOA.[l] Because of the way that the blood samples were obtained by the State, although with the aim of identifying a representative cross-sectional sample, the results do not fully reflect the complete impact of the exposure from the Saint-Gobain emissions.

The total of 472 serum-PFOA concentration results ranged from a low background at 0.3 µg/L to a dramatic high of 1,125.6 µg/L. The geometric mean was 10.1 µg/L, as compared to a geometric mean of 2.1 µg/L for the Centers for Disease Control's (CDC) data for the overall U.S. population in 2011-2012 [30]. The normal range is quite narrow, with a 95th percentile of 5.7 µg/L, while the Bennington results show 157.8 µg/L as the 95th percentile, i.e., that 5% of the residents have serum concentrations above this level. The blood serum values of the representative plaintiffs are also very high and range between 24.8 µg/L and 305.1 µg/l.

As discussed in Section III.C, U.S. general population exposures to PFOA and other PFASs do not originate from natural sources. Thus, any exposure is anthropogenic. In particular, many communities are affected by releases from local production facilities. In our recent study of EPA data on drinking water contamination, we showed that millions of Ameericans live in water distribution areas where the PFAS guideline of 70 ng/L is exceeded [31]. Although more recent data from EPA have lowered this proportion [5], it is clear that Americans are not just exposed to ubiquitous background pollution. Thus, the upper 95th percentile of blood concentrations in U.S. residents may well represent the effects of local drinking water contamination. Of note, serum concentrations of PFASs other than PFOA did not seem to be elevated in the Zone of Contamination.

Exposure patterns change with time. Eight major producers participated in the phase-out of PFAS emissions, through an agreement with the EPA, with the aim of reducing and then eliminating global emissions and product content of PFOA and related chemicals. For the period 2013-2014, the average had actually decreased by 5% [32], as compared to the previous cycle. Still, environmental dissemination of and human exposure to the PFASs are anticipated to continue for the foreseeable future due to the persistence of PFOA and other PFASs already disseminated in the environment, their redistribution and their continued formation from precursor compounds [33]. Thus, the cumulated PFOA burdens of Bennington residents (past and present) will remain elevated for many years to come.

C. Definition of class of exposed residents

I understand the class definition in this case[m] requires that members (1) have resided in the Zone of Contamination and (2) have ingested PFOA-contaminated water in the Zone of Contamination and who (3) have suffered accumulation of PFOA in the body at above-background levels. In regard to the latter, I understand that exceedance of the median serum-PFOA concentration in the U.S. population in 2011-2012, i.e., 2.1 ng/mL, is considered to be evidence of excess exposure that is associated with an increased risk of adverse health effects. As I shall show in Section VIII, adverse effects have been amply demonstrated in populations with background exposures, and it is therefore reasonable to conclude that these elevated exposure levels are associated with an increased risk of adverse health effects.

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[l] Vermont Department of Health. Results of Blood Testing and Exposure Assessment, op.cit.
[m] Third Amended Complaint [Doc. 113].

When comparing with CDC's exposure data for the U.S. population, it is necessary to consider that current exposures to PFASs do not originate from natural sources and must be considered a result of anthropogenic activities. Thus, many communities are affected by releases from local production facilities, which should not be considered as a normal background. In a recent study of EPA data on PFAS contamination of drinking water nationwide, about 6 million residents of the water distribution areas covered had highly elevated exposures, i.e., exceeding the EPA guidance level of 70 ng/L [31]. Extrapolation to areas without any water analyses available would result in substantially higher numbers. Although more recent data from EPA resulted in lower estimates [5], it is clear that many Americans are not just exposed to background pollution, but also to point sources. Thus, although defense expert Professor Guzelian refers to the 95th percentile as a preferred limit for elevated exposure (see Guzelian at 19), this recommendation is clearly inappropriate.

V. METHODOLOGICAL ASPECTS IN RISK EVALUATION

A. Interpretation of epidemiology studies

In evaluating the evidence on PFASs, a weight-of-the-evidence approach must be used, where observational epidemiological studies contribute substantially. In connection with my service as member or chair of working groups of agencies, such as the IARC, or the EFSA, I have substantial experience in evaluating the weight of different types of evidence. In principle, it would be desirable to rely on evidence that is as complete as required for decisions on evidence-based medicine. However, in a real-world situation, where the goal is to avoid risks from preventable hazards, and where human experimentation is unethical, less comprehensive documentation is generally accepted as the basis for prudent decision-making.

In the absence of human experimental studies in humans with substances that may cause cancer or other serious effects, such as PFOA, the main human epidemiological evidence comes from observational studies of occupational cohorts and from community studies of subjects exposed at different levels, i.e., so-called background levels and above, e.g., through contaminated drinking water. Luckily, as is the case in Bennington, blood concentrations of persistent compounds like PFOA can be relied upon as valid exposure biomarkers.

The evidence on human PFOA toxicity is reviewed below to respond to two of the defense experts' major arguments, i.e., to establish general causation for the elevated PFOA exposures amongst the Bennington Exposure Class leading to adverse health outcomes and to assess the justifications for Dr. Ducatman's recommendation of medical monitoring for such adverse outcomes in the exposed Bennington population. Additionally, as the defense experts' opinions on causation and on "evidence-based toxicology" are inconsistent and not in accordance with real-world risk assessment, thus requiring that I cover the methodological aspects in some detail.

1. Early occupational studies

The published occupational studies mainly regard males and are generally cross-sectional, with only few providing follow-up over several years. In some studies, blood analyses provide information on accumulated exposure levels at the point of time where the blood was

drawn, sometimes measured as the total organic fluoride (TOF) concentration. Some articles report on medical monitoring data, but the statistical analyses appear erroneous or biased.

Information from cross-sectional or prospective studies of worker populations exposed to highly increased levels of PFOA and other PFASs is useful, though can be complex to interpret. For example, follow-up studies of workers can show an overall mortality deficit [35-37], i.e., that the exposed workers lived longer than expected for the general population. Further, an easily available comparison group, e.g., the U.S. general population may not be appropriate, if a disease, such as prostate cancer, occurs at a different (lower) rate in the background population of Minnesota, as compared to the U.S. as a whole. In addition, deficits in mortality or morbidity should not necessarily be interpreted as a sign that PFAS exposure is beneficial to health, but rather that the exposed population, at least at the time of first hire, was in a better health condition and with better longevity prospects than the background population, which includes the non-working population, some of whom may suffer from chronic disease or otherwise have an increased mortality risk. Such selection bias is well established. Although it does not affect all health outcomes uniformly, the healthy worker effect demands critical assessment of relative risks, not just those that may show a statistically significant excess, but all outcomes [38]. Both total cancer and prostate cancer were elevated in the two groups when compared to Minnesota rates. The findings are similar to an article published in 1993 by Dr. Frank Gilliland and a 3M epidemiologist [35].

Partial adjustment may be achieved by using occupational comparison groups that have not been exposed to PFASs or other hazards. Another local occupational group might avoid "healthy worker" selection bias and geographical differences, but one must then make sure that the comparison group is not exposed to some other toxicants. As an optimal comparison group may not be available, it may be preferable to show the results from the exposed population in comparison with more than one reference population and to identify the strengths and weaknesses of such comparisons.

As a further concern, mortality statistics are limited by numbers of deaths and provide little information about diseases that are rare, occur mainly in the elderly or that are not reflected well by mortality data that may not include all contributing conditions at the time of death. As an alternative, some studies use clinical pathology tests or other diagnostic means obtained at a particular point in time, to uniformly establish disease or risk markers, although such data may sometimes be complex to interpret in terms of long-term health implications.

Most occupational health studies were published under the auspices of a major PFAS producer. As I shall describe in further detail below (e.g., section VIII.D.1), some of the published articles reach optimistic conclusions that appear not to be justified by the results presented in the article [39]. I also note that an internal document from this company reveals that the purpose of scientific publication was to show "that there is no medical or scientific basis to attribute any adverse health effects to 3M products."[n] Accordingly, the existence of this type of publication bias in the occupational health studies must be considered.

[n] Science publication strategy, PTX1535. Available from https://www.ag.state.mn.us/office/contactus.asp

2. General population studies

Highly relevant information regarding environmental health risks often originate from prospective studies of cohorts generated within the general population. For PFASs, this can mean either local communities affected by contamination of drinking water and other emissions from production facilities or from ranges of more general (or background) environmental exposures. Many studies are cross-sectional, but the validity of serum-PFAS concentrations as long-term exposure biomarkers is supported by the long elimination half-life of PFASs, and such studies should therefore not be disregarded. Nonetheless, prospective studies often can be more useful, e.g., because exposures during vulnerable windows of development can be better linked to changes in health.

Accordingly, birth cohorts are crucial, as they can reveal impacts of exposures during early lifetime, but such data are often limited in numbers, and long-term follow-up studies are expensive and of course take a long time. Thus, while many human studies have focused on gainfully employed adult males, only a small number of published articles relate to developmental exposure and vulnerable subgroups such as pregnant women and children. The limited extent of prospective information on exposed birth cohorts is unfortunate, as it is not just the dose that can matter but also the timing of the dosing in regard to the developmental stage of the subjects [40]. As illustrated by laboratory animal data, developmental exposure to PFOA induces effects that are not necessarily seen in response to exposures during adulthood [41].

Many studies, also in exposed communities, may still be limited by uncertain chronic PFAS exposure information (e.g., because early exposure measurements or estimates, when available, may have been inaccurate). Studies with prospective information on exposure levels are few. Again, data regarding prenatal or childhood exposures remain scant at this point. A further concern is that exposures are usually mixed, and it may be difficult to distinguish between effects attributable to particular PFASs, unless PFOA is the dominant toxicant. However, the presence of such limitations and perhaps absence of statistical significance in individual studies should not be misinterpreted as evidence that PFAS exposures are innocuous. On the contrary, in evaluating the weight of the evidence, the question must be asked what each study could potentially reveal, given the design and choice of study parameters.

Similarly, the absence of evidence on some aspect of PFAS toxicity should not be misinterpreted as proof that PFASs lack this toxicity. An expert group appointed by the National Research Council (NRC) refers to this erroneous conclusion as the "untested chemicals assumption" [42]. This is a main problem with all three defense expert reports – they assume that no risk is present at all if the evidence is not convincing to them, and they raise inappropriate critique against studies that in my mind represent strong evidence.

3. Bias toward the null

In the field of epidemiology, there is a well-known and often misleading bias toward the null, of which epidemiologists (and readers of epidemiology reports) need to be careful, especially when public health is at stake. Studies that do not show a statistical significance are sometimes called "negative" or "null," although this is misleading. A better word is non-informative (although this is not accepted by the defense experts). Joint analyses of

several such studies might well show a significant difference or trend. Table 1 highlights common causes of bias toward the null in epidemiological studies, i.e., reasons that a study might not show the existence of a risk that indeed is present, though hidden due to the bias. These are all relevant to reports by 3M authors, including Professor Mandel. While biases in the opposite direction also exist, they are usually of much less significance [43].

Table 1. Causes of bias toward the null in epidemiology studies [43].

Inadequate statistical power in small studies
Lost cases and inadequate follow-up for long-term effects
Exposed or otherwise inappropriate comparison (control) group
Exposure misclassification
Insensitive or imprecise outcome measures
Failure to adjust for confounders with effects in the opposite direction
Disregarding vulnerable subgroups
5% probability level to minimize risk of false positives (Type I error)
20% probability level to minimize risk of false negatives (Type II error)
Pressure to avoid false alarm

The bias toward the null is particularly problematic where human health is concerned; scientists and public health officers therefore often assess and rely on the direction or weight of the evidence and not solely on statistical significance, as it may take a very long time to obtain complete and irrefutable proof. Thus, observational studies will rarely if ever provide a 100 percent proof, and it is always possible for someone critical of the weight of the evidence to raise some type of doubt seeking to require additional or improved data before a conclusion can be drawn [44, 45]. It is important to repeat that the presence of uncertainties often tends to cause underestimations of actual risks, not the opposite, and this issue is of importance especially regarding substances that have not yet been studied in the detail desired. Again, many unfortunate past errors in regard to industrial chemicals have shown that initial assessments were erroneous and led to an underestimation of the true risks [46].

In the present report, while considering the extent of possible biases, my conclusions are stated in terms of assessing whether elevated exposure to PFOA results in an increased risk of injury or illness. In many instances, the existing evidence of a hazard is much stronger than that, but I understand this to be the applicable legal standard. Like Dr. Ducatman, I shall also rely on the findings regarding the PFAS contamination in WV-OH, where “probable link” assessments were requested by the court and then provided by the C8 scientific panel in its reports. I note that subsequently published research evidence has generally added further support to the probably link conclusions. My evaluation as an expert therefore considers the uncertainties involved, the plausibilities and what could possibly be known, given the study opportunities and methodologies applied.

B. Toxicity and interpretation of data

In the absence of randomized clinical trials on PFASs, the hazard evaluation must be based on observational epidemiology studies. Thus, I shall also examine the toxicological evidence from animal studies to evaluate the plausibility of the epidemiological findings, i.e.,

whether or not their plausibility is supported by the experimental evidence. Still the toxicology studies carried out do not necessarily cover all desirable endpoints as well as dosages and species, and some adverse effects seen in humans are not yet supported by toxicology studies.

The research evidence must be considered in light of both strengths and weaknesses. While a methodological failure may weaken the support for a particular association, the mere occurrence of some scientific weakness does not prove the absence of a risk. Unfortunate and erroneous rejection of warning signals has occurred in the past because of presumed confounding or other biases, and uncertainties [46]. Thus, statistical acceptance of the null hypothesis should never be interpreted as proof of safety. Further, effects within normal variability should not be disregarded, since a population-wide shift in the distribution may cause substantial harm. The focus should be on populations at risk rather than averages that are diluted by the results of non-vulnerable groups [43].

C. Medical surveillance and screening

Criteria have been developed for targeted medical monitoring of exposed populations exposed to significant hazards, at first under the auspices of the World Health Organization, then updated [47, 48], and later revised under the auspices of the National Institute of Occupational Health and Safety [49]. In agreement with the criteria listed, elevated PFAS exposures are linked to an increased risk of important health problems, including immune system dysfunction, reproductive dysfunction, endocrine disruption, including increased risk to thyroid disease and diabetes, liver dysfunction, and increased risks of cardiovascular disease and certain types of cancer. Early detection of latent disease is possible and can lead to treatment of known efficacy.

Dr. Ducatman's recommendations for medical monitoring meet these criteria. For the Bennington PFOA-exposed community, diagnostic testing is reasonably necessary, given the well-documented excess exposures. Contrary to the contentions of defense experts, this monitoring should be carried out without regard to the residents' prior health or other risk factors, as the exposure-dependent disease risks have been identified in the general population, i.e., without regard to other risk factors. Thus, my assessment of need for medical monitoring is based on exposures created by Saint-Gobain in the Bennington Zone of Contamination and do not depend on individual states of health.

VI. KNOWLEDGE ON HEALTH EFFECTS

I outline in this section the general development over time of PFAS-related research. I also touch upon key studies and reviews to outline how information was obtained over time and how knowledge was pursued (or wasn't) over time. As is common in modern risk assessment, I shall stick to a weight-of-evidence approach in this presentation, while considering the weaknesses and concerns outlined above.

A. Growth of PFAS research

Even though PFASs have been produced for over 60 years, independent publication on PFAS toxicity only began in earnest about 10 years ago [50]. The broader scientific community, therefore, is still at an early stage of understanding about how human exposure to these compounds affects health. For example, chronic toxicity studies have been published only based on rats [8]. A formal cancer bioassay is still missing [7]. In addition, insufficient attention had been paid to exposures during sensitive developmental stages. I note in particular that few epidemiology studies have focused on exposures during infancy or prenatally, although early development must be considered a highly vulnerable period that must be taken into regard when determining exposure guidelines [51]. One again, I must emphasize that the incomplete toxicology coverage means that the spectrum of adverse effects from PFAS exposure is most likely underestimated, as absence of information does not mean absence of toxicity.

Since the first reports in scholarly journals that revealed widespread global occurrence of PFOS in wildlife [52] and the detection of PFASs in blood from the general population [53] were published about 2000, the scientific literature on the environmental and toxicological aspects of PFASs has increased, and the annual number of publications on the PFASs now exceeds 400 [54]. Still, by comparison, the quantity is less than for many other chemicals for which there are also human health concerns. Most of the published articles on human health risks from PFASs are fairly recent. When we examined the 120,000 articles published in the 78 major journals within the fields of environmental science, toxicology and public health during the first 10 years of this millennium, we found only 271 articles that referred to PFOS and a slightly higher number (363) on PFOA (most of the articles being the same) [50]. For comparison, the twenty most mentioned environmental chemicals (e.g., toxic metals, PCB, and PAHs) were each covered in over 2,000 articles during this period, lead alone was dealt with by close to 1,000 articles each year. Thus, PFASs were not a research priority in environmental health, at least up to 2007, as also seen in Figure 1 (page 17).

Accordingly, the intensive focus on PFASs in scientific publications happened during the most recent 10 years, thus emerging decades after the first discoveries of PFAS toxicity. Also, the reports from the court-mandated C8 studies, described below, are very recent and mainly relied on cross-sectional study designs, although fortunately on large population groups in most cases. Since then, a substantial number of prospective studies have emerged, although this has not been acknowledged by the defense experts (see Calabrese at 7: “the overwhelming majority used a cross-sectional design”).

The evidence at hand is therefore fairly recent and unlikely to represent the full toxicological perspective, such as those that may occur at a delay, and some adverse effects and vulnerable subpopulations may not yet have been identified. The occurrence of adverse effects at chronic exposures to low PFAS levels still needs to be explored in greater detail, especially regarding the long-term effects of developmental exposures. As has been seen on numerous occasions [46], the evidence available today is therefore likely to underestimate the true extent of the PFAS toxicity.

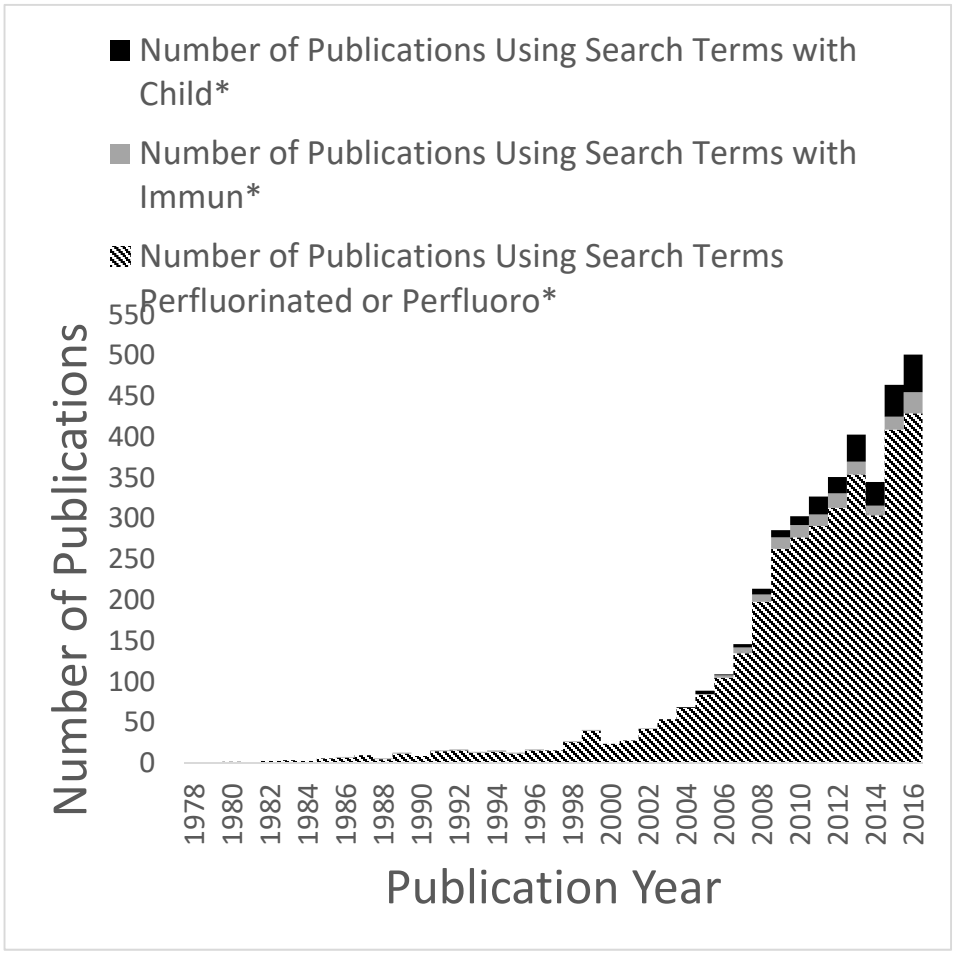

Figure 1. Number of publications on PFASs over time, according to the Web of Science database (between 1978 and 2017), using the search terms "perfluorinated or perfluoro" and restricting to environmental sciences, toxicology, or public, environmental, and occupational health categories. This search was further refined further using the search terms "immun*" and "child*".*

B. Recent reviews and assessments

I mention here certain recent key reviews and studies. In my discussion of particular endpoints, in the next section, additional reviews and studies are referred to. The expert reports by Dr. Ducatman contain substantial information on adverse health effects and also appropriately relies on the major reviews. The conclusions from these reviews reflect the real-world approach to risk assessment, not the approach used by the defense experts, who aim at disregarding all evidence that supports a causal relation between PFAS exposure and adverse health outcomes.

1. C8 Science Panel

General population studies addressing PFASs mainly have been cross-sectional, but important research data have emerged from the Mid-Ohio River Valley population, where PFAS contamination of drinking water occurred. The final conclusions of the C8 Science Panel, as submitted to the Court, refer to the probable links of the PFAS contamination and plausible adverse effects regarding cancer and several other important health conditions. The C8 Panel carried out several large-scale studies, although most of them focused on PFOA. The Panel

concluded that PFOA exposure was probably linked to six important health conditions, including two types of cancer [9].

In somewhat greater detail, the West Virginia Circuit Court in 2005 approved a class action Settlement Agreement in a lawsuit about releases of PFOA from DuPont's production facility in Wood County, West Virginia. The Settlement created a Science Panel of three epidemiologists that was to conduct research in the community to evaluate probable links between PFOA exposure and human disease.

In addition, a C8 Health Project was established to collect data from Class Members through questionnaires and blood testing. This community health study includes approximately 70,000 Ohio and West Virginia residents with at least one year of exposure to drinking water contaminated with PFOA from about 50 ng/L to over 3000 ng/L. Data on serum PFOA concentrations provide information on the relationships between external dose from drinking water and the internal dose, i.e., the serum concentration, and a variety of biological changes. The median serum-PFOA concentration for all participants was 28 ng/mL, and the median in the highest decile (the subjects with the highest 10% of exposures) was 482 ng/mL.

These data, and the conclusions released by the Science Panel, constitute an important basis for the present report. Based on the results from these studies and an evaluation of the literature, the Science Panel delivered reports on 'probable links,' as summarized in the final report from 2012. The C8 Panel determined that exposure to PFOA had probable links to adverse effects on the following human health conditions (Table 2).

Table 2. Adverse human health conditions, where 'probable links' to PFOA exposure were identified by the C8 Panel [55].

- Ulcerative Colitis
- Pregnancy-Induced Hypertension/Preeclampsia
- Thyroid Disease
- High Cholesterol
- Kidney Cancer
- Testicular Cancer

Although the reports to the Court were not peer-reviewed at the time and only provide a brief summary of the new study results, most of the evidence has since then appeared in peer-reviewed scientific journals, which will be referred to below. As seen in Figure 1, the most recent five years have seen about as many publications on PFAS toxicology as in the years up to the completion of the C8 report. Dr. Ducatman relied on such evidence and added other outcomes supported by recent evidence.

2. Other major assessments

The PFASs have been the focus of a variety of evaluations carried out by regulatory agencies, most recently by the U.S. EPA [56], the ATSDR [5], and the EFSA [28]. I shall rely on these report and also on the reviews on particular aspects generated by the NTP on immunotoxicity [6] and by the IARC on cancer risks [7]. These sources refer to a wider range of

studies than the present report, where the focus is on human health regarding PFOA exposures occurring in Bennington.

In the absence of human experiments on PFAS toxicity, which would of course be unethical, agencies often choose to rely on experimental studies in laboratory animals to generate risk assessments and to reach conclusions on safe exposure limits for single PFASs. While this has been a long-term tradition for these purposes, the present report evaluates the weight of the epidemiological evidence on adverse effects of PFAS exposures in the light of supporting toxicity evidence to determine whether elevated exposure to PFASs, and PFOA in particular, results in an increased risk of illness or disease.

VII. OPINIONS OF THE DEFENSE EXPERTS

A. Expert background

The three defense expert reports are similar in their refusal to accept causal associations between PFOA exposure and adverse health outcomes. This report's previous sections describe proper evaluation of toxicity risks, as used by regulatory agencies and international organizations like the WHO. However, crucial aspects appear to be contested or ignored by the three experts, who instead refer to their own methodologies whose aim is to disregard any evidence of causality.

The defense experts make exaggerated claims, such as "the strength of the statistical association is typically meager and the effect relating to PFOA exposure is typically small in magnitude" (Mandel at 4). Another claim is that Dr. Ducatman "did not cite all available studies" (Guzelian at 13), which is unreasonable given the numbers of publications available by now (Figure 1), especially since the focus should be on those that carry substantial weight to elucidate the possible occurrence of adverse human health effects. Further, one defense expert concludes that "the studies cited in Dr. Ducatman's reports are dominated by research methods that cannot be used to assess causal relationships" (Calabrese at 25). It is hard to understand this harsh critique. On the one hand, defense experts (unfairly) criticize Dr. Ducatman for not using appropriate methodology when evaluating the evidence. However, on the other hand, they fail to justify their own conclusions.

I shall comment on individual aspects of the critiques below. I note that only two of the three experts have contributed to research on PFASs. I shall first summarize some comments on the individual backgrounds.

1. Jeffrey H. Mandel, MD, MPH

Dr. Jeffrey H. Mandel is currently an associate professor within the Division of Environmental Health Sciences at the University of Minnesota School of Public Health. Professor Mandel previously worked at 3M, a major producer of PFOA, where he co-authored 12 articles on occupational PFAS exposure in scientific journals, with 3M colleagues. Several were published in the Journal of Occupational and Environmental Medicine known to favor submissions from industry doctors. It is noteworthy that these articles tend to refute or downplay

any adverse effects of PFAS exposure, although it is surprising that highly-exposed production workers would not show any signs of ill health. In connection with a previous court case, several internal documents from 3M were released, including a strategy paper from 1998, i.e., at a time when Professor Mandel was employed by the company.[o] The key message of this 3M document was that the purpose of publication of scientific information was to demonstrate "that there is no medical or scientific basis to attribute any adverse health effects to 3M products." The publications co-authored by Professor Mandel seem to follow this strategy.

Among Professor Mandel's publications is a highly cited article [57] that concluded that "there were no substantial changes in hematological, lipid, hepatic, thyroid, or urinary parameters consistent with the known toxicological effects of PFOS or PFOA in cross-sectional or longitudinal analyses of the workers' measured serum fluorochemical concentrations." In support of this conclusion, the article included some descriptive tables that described quartile groups of workers, but the wording "data not shown" was used several times, and only the final Table 6 listed some results of regression analyses. The authors asserted that the statistically significant and positive associations found were likely spurious and not toxicologically meaningful.

Among the internal company documents recently released is a draft, dated October 11, 2001, of the published article.[p] This draft lists the same authors and concludes – in opposition to the published paper – that there was a positive association between PFOA and serum cholesterol and triglycerides over time, as based on 20 tables with regression results. Only partial results without *p* values from four of the tables were included in the published article [57]. Given that many subsequent studies of communities exposed to PFASs have shown elevated serum-lipid concentrations and other serum abnormalities at much lower exposures [58-60], adverse associations in PFAS production workers would be anticipated and considered plausible.

In line with the conclusions in this article, Professor Mandel also now rejects any association between PFAS exposure and adverse health outcomes. Professor Mandel states in his report: "The existing epidemiology of PFOA, consisting of worker exposures, general population exposures and exposures from environmental exposed communities has not identified any disease with scientific certainty that causally relates to this exposure." (Mandel at 2). Thus, Professor Mandel substantially relies on his own work carried out under 3M auspices, ostensibly in fulfillment of the company strategy for desirable research.

While Professor Mandel lists strict criteria for acceptance of scientific evidence in support of a causal relationship (Mandel at 29), he does not seem to have any similarly strict criteria when considering reports which misleadingly or erroneously claim the absence of a causal relationship.

2. Edward J. Calabrese, PhD

Dr. Edward Calabrese is a tenured professor of toxicology within the Department of Environmental Health Sciences at the University of Massachusetts, Amherst, School of Public

[o] Science publication strategy, PTX1535, op.cit.
[p] Manuscript, Bates pages 3M-MN02482163-225, PTX1799. Available from https://www.ag.state.mn.us/office/contactus.asp

Health and Health Sciences. Professor Calabrese is a prolific writer and has published over 800 papers, including numerous articles on a phenomenon that he calls "hormesis." This term implies that very small doses of an environmental hazard, such as ionizing radiation, may lead to a small advantage, rather than a disadvantage, thereby deviating from the hypothesis of monotonic (or linear) dose-effect curves. He has particularly emphasized evidence on ionizing radiation as support for this idea, and Professor Calabrese has frequently written about other such evidence that he finds in support of his hypothesis. Some of his articles are published in journals well known to favor submissions from industry toxicologists (such as Critical Reviews in Toxicology and Regulatory Pharmacology and Toxicology), but also in less prominent journals like Homeopathy, from the Faculty of Homeopathy.

I note that Professor Calabrese is much less critical of evidence in support of "hormesis" than evidence in support of PFAS toxicity. Professor Calabrese has repeatedly and eagerly defended his interpretation of radiation evidence at low doses [61]. While severely criticized [62], he has apparently not changed his mind on low-level hormesis. Nonetheless, he now writes: "Even in the most studied subjects, such as with ionizing radiation, where many thousand animal model studies exist and a voluminous human epidemiological literature also exits, there remain recognized and generally accepted uncertainties in which risks from low level exposures cannot be discerned from background" (Calabrese at 6).

In his report, Professor Calabrese includes a 6-page list of literature references that he considered, but also a 48-page list of "additional" references that include many of the key studies on PFAS exposures and human health risks. It is not clear how Professor Calabrese decided what to consider and to cite, and how he justified his opinions without relying on most of the key studies and authoritative reviews. For comparison, his "hormesis" theory on effects of low-dose exposures has been challenged numerous times [62-65], but the critique, in his view, is unjustified and not in accordance with his data and interpretation of data that may appear uncertain. Thus, it is not at all clear why he would now so strongly oppose the evidence on low-level PFAS toxicity.

According to the Web of Science, Professor Calabrese's work has been cited several thousand times over the years. However, about 20% of the total are auto-citations, i.e., where the author cites his own work. Although Professor Calabrese participated in the WHO's large project to develop a (750-page) manual on "Principles and Methods for the Risk Assessment of Chemicals in Food" [66], the volume does not refer to "hormesis" nor does it cite any of Professor Calabrese's publications.

The discussion on the curve shape for dose-effect relationships continues, but there is little focus today on "hormesis." Rather, a report from the WHO on endocrine disrupting substances highlights a very different phenomenon that also violates the monotonic curve shape [67]. In this case, however, important evidence shows that, below apparent thresholds for effects, very low doses may in fact have adverse effects, despite the dose being below levels considered safe. This is the opposite of Professor Calabrese's hypothesis. The contrast is important, as PFASs are considered endocrine disruptors (as discussed in Section VIII). Thus, while "hormesis" has inspired many discussions, today's researchers in the field are more concerned about adverse effects, rather than beneficial stimulation, at very low doses. It is surprising that

Professor Calabrese has for many years defended his own interpretation of low-dose changes, while he now seems to argue that they can't be proven.

3. Philip S. Guzelian, MD

Dr. Philip Guzelian is a retired clinical professor of medicine from the Departments of Medicine and Pharmacology at the University of Colorado, Denver, Health Sciences Center, where he served also as Chief of the Section of Medical Toxicology for 17 years. Professor Guzelian (like Professor Calabrese) has apparently not published on PFASs and seems not to have been scientifically active in the most recent years, although he lists 127 scientific articles up to 2006. Among his important achievements, he was the editor of a meeting report on "Similarities and differences between children and adults", published by the International Life Science Institute (ILSI, a non-profit organization known to rely on industry support) [68]. The main conclusion of this meeting was: "Differences in sensitivity between children and adults are chemical specific and must be studied and evaluated on a case-by-case basis," i.e., that there is no need to protect children and the fetus, unless there is proof that this is necessary. However, this conclusion is counter to the recommendations of a National Research Council (NRC) report that was published the following year [69]. The NRC expert committee reviewed the need for special protection of children against food contaminants and concluded that a 10-fold safety factor would be required for protection of this vulnerable population, and that this was required even in the absence of a formal proof.

Professor Guzelian has for many years promoted his ideas about evidence-based causation in toxicology [70]. However, these ideas have been forcefully challenged [71]. Thus, Professor Guzelian in his rebuttal refers to the very strict criteria for use of scientific data in evidence-based medicine, as applied in regard to proof of therapeutic effects (of drugs for beneficial human use). His mistake is to apply the same criteria in "evidence-based toxicology" regarding proof of harmful effects, in this case caused by preventable environmental exposure to industrial chemicals like PFOA. This stringent approach has not been adopted by regulatory agencies.

Professor Guzelian refers to so-called "Hill Criteria". However, British biostatistician Austin Bradford Hill referred to aspects, not to criteria [72]. I shall return to this issue below. Rather than following Sir Austin's advice, Professor Guzelian seems to mistake the validity of his own conclusions for meticulousness in identifying presumed violations of the causal "criteria" committed by Dr. Ducatman in his reports.

B. Issues of concern in the defense expert reports

1. Assessment of causality

Severe critique may be considered appropriate for highly respected experts and may appear in accordance with their high methodological standards and unrelenting skepticism to the work by (younger) colleagues. However, a narrow focus on scientific methodology is often coupled with blindness to environmental degradation and social injustice. Not surprisingly, the strategy of criticizing research methodologies has been vigorously explored by vested interests, often with the purpose of manufacturing doubt [73]. Although it may serve an educational

purpose to demand an almost unrealistic quality level of research, it usually aims blocking prudent risk management while paving the way for potentially toxic chemicals to be released into the environment.

Professor Guzelian's article on "evidence-based toxicology" seems to fit this characteristic [70]. It has been cited close to 100 times in the scientific literature, often by industry-affiliated colleagues, who require a literature reference to justify dismissal of studies that contain unwelcome conclusions. However, some academic sources are critical of the overly strict approach that dismisses so much relevant evidence [71, 76]. This critique is not addressed by Professor Guzelian, who, in his report, repeatedly refers to his own article and, on occasion, to a couple of other previous sources, as justification of his approach and of his critique of Dr. Ducatman. However, the auto-citations by no means offer support that his approach is generally accepted or in accordance with mainstream toxicology and regulatory assessment.

In an article that I co-authored with a prominent international group of epidemiologists [77], we wrote: "It is of interest that in the alleged spirit of epistemologic modesty, such slogans as "sound science" and "evidence-based toxicology" have been put forward by professionals with a record of collaboration with the tobacco industry (Guzelian et al. 2005). The purpose has clearly been to dismiss evidence from animal models and only accept "conclusive" epidemiology on risks in humans (Ruden and Hansson 2008), effectively cutting off a line of important evidence for risk assessment." This assessment appears appropriate also now, ten years later, and likewise Rudén and Hansson's critique [71].

In general, one can easily agree that the quality of the existing evidence needs to be considered, as I have done in this report. This is important, both for studies that appear to show an exposure-effect relationship and those that do not, such as Professor Mandel's publications. Likewise, the validity of laboratory models must be considered in regard to their relevance to human health, but they should not be ignored just because they refer to the wrong species. However, Professor Guzelian's approach is extreme, as he dismisses key epidemiological studies one by one, and he also ignores recently published prospective studies of high quality. The two other experts have adopted a similar approach, although without relying on Professor Guzelian's 2005 article (that he himself considers the basis for risk assessment). While they criticize Dr. Ducatman for selective citing of the literature, the defense experts are much more selective when they ignore high-quality prospective studies that disagree with their own preferred conclusions.

In line with the arguments raised by the defense experts, a call was issued several years ago for "Good Epidemiological Practice" as a useful tool to stimulate high quality (and "sound") science. However, strict interpretation of epidemiological rules was soon applied in order to disregard epidemiological findings that seemed unwanted by vested interests. It turned out that the initiative originated with industry groups [78].The scientific rigor that had been considered a prerequisite in the traditional science paradigm was now turned around and became an unrealistic requirement for repetitive, controlled studies that could furnish virtual statistical certainty. Using strict criteria, unwanted results could more easily be criticized as "junk" science and any uncertainties were erroneously interpreted as an indication that no hazard was present.

As I have outlined above, given the substantial excess exposure to PFOA in the Bennington community, it would be unreasonable to insist that the exposure is innocuous simply because some experts are not convinced about the details of the evidence. As described in the "Late lessons of early warnings" project of the European Environment Agency [46], several optimistic assumptions were, at first, considered valid and important, but were later found to be misleading and in fact dangerous to human health. Table 3 shows some of these assumptions that were later found to be unrealistic and counter to public health [43].

Table 3. Assumptions commonly made in risk assessments on incompletely documented environmental hazards, as compared with evidence emerging at a delay [43].

Initial assumption	**Late scientific lesson**
Presence of environmental chemicals in the body can be tolerated at "safe" or "natural" doses	Delayed effects, cumulated or re-mobilized doses, or toxic metabolites may occur at exposures previously thought to be safe
Absence of harm in adult male workers (from routine medical data or mortality) reflects the absence of risk to the general public	Subpopulations, such as children and the elderly, may be more vulnerable to the exposure
Biological changes may not necessarily be adverse and can be considered harmless	Definite adverse effects may develop later on
Dose-response relationships are consistent (and monotonic), and no risk occur at low doses below an apparent threshold	Some substances show low-dose effects that are not readily predictable from responses to high doses
Short-term assessment of exposures from a single pathway can generally be considered sensitive and valid	Most methods for exposure assessment are imprecise, and imprecision generally results in underestimation of the toxicity
The placenta and the blood-brain barrier amply protect sensitive life-stages and organs from toxic chemicals	The barriers may be bypassed, and they offer limited protection against industrial chemicals
Average findings in exposed subjects indicate the potential for harm to the exposed population	Sensitive sub-groups may show effects that are not apparent from the average data
Toxicity evidence from animals is not relevant to human toxicity	Humans may be more vulnerable to some toxic effects than other species

2. Weight of the evidence and Sir Austin's "criteria"

The defense experts' reports properly emphasize the importance of prospective studies, where the exposure is measured on an earlier occasion and then the suspected adverse effects identified at a later time. Apart from ignoring a solid collection of prospective studies that I have cited in the following section, their critique of the evidence is exaggerated: "the strength of the statistical association is typically meager and the effect relating to PFOA exposure is typically small in magnitude" (Mandel at 4). Another report claims: "Simply put, the studies cited in Dr. Ducatman's reports are dominated by research methods that cannot be used to assess causal relationships" (Calabrese at 25).

Similarly, the adverse health outcomes identified as effects of PFOA exposure are dismissed: "Changes in health endpoints (e.g., cholesterol, liver enzymes, thyroid function) have been reported as associated with PFOA in some studies, but the changes in endpoints have remained in or close to the normal range for those tests. (…) The impact of these small changes has not been clearly established from a clinical perspective." (Mandel at 4). I find it hard to believe that a toxicology expert would want to ignore an elevated serum-cholesterol or a deficient response to a childhood vaccination.

All three defense experts put much emphasis on the "Bradford Hill criteria" (in particular, Mandel at 29 and Calabrese at 13, Guzelian at 17 in Appendix B). However, Sir Austin did not use the word "criterion", but referred to aspects and viewpoints, while emphasizing his nine "examinations" as useful "if available and applicable" [72]. Thus, Hill did not intend his nine concerns to be employed as a checklist of causal criteria, and most epidemiologists reject the idea that causation can be established by satisfying a simple list of qualitative conditions [79-81]. In contrast, Sir Austin underlined that certainty must be expressed in degrees and that, depending on what is at stake, different degrees of certainty about causality are required for taking action.

A common strategy is to disregard studies that do not satisfy certain methodological criteria, sometimes exaggerating alleged "criteria" for causality. Although such criteria can be useful, as addressed above, Sir Austin noted: "All scientific work is incomplete…All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us the freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at the given time" [72]. Nonetheless, the defense experts appear to support the purported validity of their own conclusions by alleged violations of the causal "criteria" and other validity requirements that, allegedly, have been committed by Dr. Ducatman and apparently also by authors of regulatory agency assessments (which are generally ignored by the defense experts).

The use and misuse of the mislabeled Hill "criteria" was recently discussed in much detail in the journal *Jurimetrics* published by the American Bar Association [82]. Of note, Hill, being a biostatistician, advised against significance testing as an answer to questions on causality. Further, his causality aspects are asymmetric: Although affirmative answers may support causality, none of them is a necessary condition (perhaps apart from the temporal relationship), and the lack of one or more affirmative answers does not speak against causation. This treatise is firmly based on biostatistical inference, epidemiological interpretation, and biological reasoning.

The *Jurimetrics* authors write: "The existence of "null" studies, or studies with elevated risk ratios that do not attain statistical significance at the .05 level, are often erroneously considered as supportive of no causal relationship by attorneys and their expert witnesses, regardless of their potentially low statistical power and the difficulty of proving that no effect of policy or legal relevance exists. These claims are counter to the recommendations of Hill, who specifically inveighed against requiring statistical significance, explicitly aimed at the best explanation, and pointed to a weight of evidence approach that considered the results of other available examinations" [82]. Again, this statement is in accordance with modern epidemiology [81] and also agrees with my own experience in risk assessment and agency evaluations. The

May, 2018, issue of the American Journal of Public Health featured a discussion on causal inference [83]. As expected, opinions varied somewhat, but no one expressed support for prohibitive criteria as voiced by the three defense experts. Clearly, the defense experts deviate from this real-world reasoning and provide no justification for their extreme views.

3. Prudent choice of evidence or "cherry-picking"

The defense experts criticize Dr. Ducatman for selectively citing the literature and only referring to studies that are in accordance with his conclusions. If that were indeed the case, that would be dishonest and misleading. It would not be in accordance with the strength-of-the-evidence approach that I have described above. But the critique itself is misleading and inaccurate.

As can be seen from Fig. 1, the number of relevant publications has fortunately increased substantially, and it would be an enormous task to review them all. We therefore rely on reviews and evaluations carried out by regulatory and research agencies [5, 6, 28, 56]. That allows us to focus on the key studies that carry the most weight. Indeed, the defense experts have largely ignored the governmental reviews, and they have further missed some important prospective studies.

To illustrate Dr. Ducatman's alleged "cherry-picking", Professor Calabrese refers to "[n]umerous examples (Boudreau et al., 2003; Coperchini et al., 2015; Florentin et al., 2011; Hagenaars et al., 2011; Henry and Fair, 2011; Liu et al., 2017; Midgett et al., 2014; Rosenmai et al., 2016; Wan et al., 2014; Wirth et al., 2013; Yao et al., 2014) exist showing no biological effects over very wide ranges of exposure" (Calabrese at 5). It is not clear why these experimental studies (mainly in vitro data, and not epidemiological) should be important enough to be included in a risk assessment, given the several thousand other references and the wealth of epidemiology information. For example, although the ATSDR considered 187 animal toxicology studies, of which 48% were on PFOA [5], only three of Professor Calabrese's 11 highlighted references were considered. Likewise, EFSA [28] decided to ignore most of Professor Calabrese's selections. Given the narrow focus of Professor Calabrese's expert report, it is hard to understand how he could accuse Dr. Ducatman of cherry-picking.

4. Dose-dependent risk

Given the erroneous conclusions of the defense experts that there is no convincing evidence of adverse health risks from PFOA exposure, it is not surprising that they consider the elevated exposures in the Bennington Exposure Class minuscule and non-adverse. However, the evidence shows that the exposures are substantially elevated. Results of blood testing have been released by the VT Department of Health in September, 2017,[q] as discussed in Sections IV.B and C.

The serum-PFOA concentration results from the Zone of Contamination ranged from a low background at 0.3 µg/L to a dramatic high of 1,125.6 µg/L. The geometric mean was 10.1 µg/L, i.e., five-fold above the mean for the overall U.S. population. The normal range is quite narrow, with a 95th percentile of 5.7 µg/L, as compared to 157.8 µg/L in Bennington. Also,

[q] Vermont Department of Health. Results of Blood Testing and Exposure Assessment, op. cit.

the serum values of the representative plaintiffs range between 24.8 µg/L and 305.1 µg/l. Further, serum-PFOA concentrations in Bennington residents are strongly correlated with PFOA levels in well water, thus supporting the notion that consumption of contaminated drinking water was the primary source of exposure to PFOA in the Zone of Contamination.[r]

As discussed in Section IV.C, U.S. general population exposures to PFOA and other PFASs do not originate from natural sources. Thus, any exposure is anthropogenic. In particular, many U.S. communities are affected by releases from local production facilities and from toxic waste. In a recent study of EPA data on PFAS contamination of drinking water, we found that about 6 million Americans reside within water distribution areas that exceed the EPA 70 ng/L guideline [31]. Data were unavailable for about one-third of the population, and a much larger number is likely affected by such contamination, also at levels below the EPA guideline. Thus, Americans are not just exposed to a general background of pollution.

VIII. ADVERSE HEALTH EFFECTS AT INDIVIDUAL ENDPOINTS

As stated above, it is my opinion that the elevated PFOA exposures suffered by members of the Bennington Exposure Class result in an increased risk of illness and disease, including at least adverse affects on human immune system functions, reproductive functions including adverse effects to the next generation, endocrine functions, including increased risk to thyroid disease, liver function abnormalities, and by causing or increasing the risk of diabetes, cardiovascular disease, and certain types of cancers. Below, I discuss the different human health hazards one by one. The first section is on immune system dysfunctions, as much evidence is now available and because these effects have not been dealt with in detail in reviews by regulatory agencies. To some degree, this is true also in regard to reproductive toxicity and endocrine disruption, while other organ systems and cancer have been dealt with in substantial detail elsewhere, and in Dr. Ducatman's expert reports, so that my coverage can be briefer.

In each of the following subsections, I discuss the epidemiological evidence that I rely on, summarize the supporting toxicological evidence, and lastly discuss possible mechanisms, and additional studies or potential criticisms relating to the endpoint in question. I have made a reasonably comprehensive review of the epidemiological evidence, and have employed a weight of the evidence approach, as is commonly accepted in the scientific community in reviewing studies on a particular topic. Thus, I have cited the most relevant studies and have not aimed at including references to studies of less validity or less strength.

A. Immunotoxicity and autoimmunity

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that elevated PFOA exposures like those suffered by members of the Bennington Exposure Class result in an increased risk of harm to human immune system functions, including an increased risk of ulcerative colitis. I am therefore in overall agreement with Dr. Ducatman's assessment.

[r] Vermont Department of Health. Results of Blood Testing and Exposure Assessment, op.cit, at 4.

The immune system is crucial in fighting communicable diseases. It is also crucial in detecting and eliminating cancer cells. In addition, the immune system is involved in allergic disease and in autoimmunity. As the adaptive immune system is programmed during early development, immunotoxicity assessment is particularly relevant in subjects with PFAS exposures during early life [84]. As discussed above, PFASs are excreted in human milk, and breastfed children may thus be particularly at risk.

The immune system is a sensitive target for PFAS toxicity, perhaps the most sensitive, as illustrated by studies of deficient antibody responses to routine vaccinations in children exposed to PFASs. This approach was recommended by an international symposium in 1999 [85] and has been used to characterize immunotoxic effects of, e.g., PCB and dioxins [86-89]. Children who are highly exposed to immunotoxicants may be unable to generate enough antibodies to provide protection against the infectious diseases against which they are vaccinated. Responses to vaccinations in terms of concentrations of specific antibodies can therefore be used to assess immune dysfunctions.

The NTP concluded in 2016 that PFOA and PFOS are likely, or "presumed to be," human immunotoxicants [6]. NTP uses the term "presumed" to denote the level of evidence just below "known," and stronger than "suspected." In addition, autoimmunity, including ulcerous colitis, was considered as a possible outcome, although with "low confidence" according to the NTP, due to the few studies available. Taken as a whole, PFOA exposure at levels similar to or below those reported from the Bennington area are associated with a range of immunotoxic effects.

As I discuss further below, prospective studies of birth cohorts have shown dramatic negative effects of PFASs regarding children's response to routine immunizations, thus demonstrating that these substances can adversely impact the development of the adaptive immune system in early childhood. A reduced or flat antibody concentration response to vaccinations has been observed even in adults of the general population at elevated serum-PFAS levels. Such effects are linked to an increased occurrence of infectious diseases, and the immune dysfunction may well have even more severe implications.

1. Epidemiological evidence

My review of available epidemiological studies demonstrates a strong link between PFAS exposure and adverse effects on human immune system functions.

a. I was the principal investigator of a study that found significant adverse impacts of PFAS exposure on indicators of vaccination efficacy in children. The first study, which was based on 656 births in the Faroe Islands followed 587 of the children through to age 7 years and found that a doubling in exposure to PFOS and PFOA was associated with an overall decrease by about 50% in the antibody concentration [90, 91]. At the same time, a substantial number of children at age 7 had such a low antibody concentration that they had no long-term protection against the targeted diseases despite a total of four vaccinations.

The antibody response to childhood immunizations is of clinical relevance and reflects major immune system functions, and in addition is a feasible parameter to use in

population studies [92]. Thus, study subjects have all received the same doses of antigen (in the form of the vaccines) at the same ages, and examinations can then be scheduled at similar ages, i.e., at similar intervals after the most recent vaccination [85]. Our particular study focused on the fishing community of the Faroe Islands, where residents with frequent intake of marine food have increased exposures to marine contaminants, such as the PFASs [93]. A major advantage of these studies is that the population is fairly homogeneous and that participation rates at follow-up remain high.

We have followed a Faroese birth cohort of 656 singleton births through to adolescence [94]. Among PFASs in maternal pregnancy serum, PFOS showed the strongest negative correlations with antibody concentrations in their children at age 5 years (after three vaccinations within the first year after birth), where a doubling in exposure was associated with a difference of -41% ($p = 0.0003$) in the diphtheria antibody concentration. PFASs in the child's serum at age 5 likewise showed clear, negative associations with antibody levels, especially at age 7 (two years after a booster vaccination at age 5 years). For doubled concentrations at age 5, PFOS and PFOA showed odds ratios (ORs) between 2.4 and 4.2 for falling below a clinically protective antibody level of 0.1 IU/mL for tetanus and diphtheria at age 7. We concluded that developmental exposure to PFASs is associated with humoral immune system deficits in humans [91]. It is worth noting that the PFOS and PFOA levels in maternal pregnancy serum and the child's serum at age 5 that were measured in this study showed concentrations similar to, or lower than, those documented in prior studies in the U.S. [30].

Of particular concern is the finding that several children at age 7 years (two years after the age-5 diphtheria and tetanus vaccination booster) had antibody levels against diphtheria and/or tetanus below the clinically protective level of 0.1 IU/mL [91, 95]. This means that the children had no long-term protection against the diseases – despite a total of four vaccinations. Adjustment for elevated PCB exposure did not materially affect the calculations, as would be expected due to the poor correlation between the two [91].

b. The findings of our above study are consistent with a smaller study carried out in Norway on a subgroup from the national birth cohort. In 50 3-year-old children, inverse correlations were found between the mother's PFAS exposure during early pregnancy and decreased antibody levels in their children against four different childhood vaccinations, with rubella showing a statistically significant decrease at higher exposures to PFOA [96]. This study also found that increased concentrations of PFOA were linked to statistically significant increases in the incidence of their children suffering from common cold and from gastroenteritis. Of importance, in these children, elevated PFAS exposures were linked to both lower antibody concentrations and more frequent infections.

c. In a more recent Faroese birth cohort, serum-PFAS concentration profiles during infancy were estimated based on the duration of breastfeeding, and the calculations were validated by comparison with measured serum-PFAS concentrations at age 18 months. At the lower PFAS exposures, inverse associations with age-5 serum concentrations of antibodies against tetanus and diphtheria vaccines were similar to those seen in the previous cohort. Concentrations estimated for ages 3 and 6 months showed strong inverse associations with antibody concentrations at age 5 years, i.e., more than four years later, particularly for tetanus. These associations were stronger than those seen for PFAS concentrations at ages 18 months and

5 years and therefore support the notion that the developing adaptive immune system is particularly vulnerable to immunotoxic exposures, e.g., to PFOA, during infancy. This finding also means that studies relying on serum concentrations that do not reflect ages at peak vulnerability will likely underestimate the true effects.

d. In addition to routine childhood immunizations, many people receive immunizations for the flu, often on an annual basis and for a specific flu variant, such as the Avian flu or the Swine flu. PFAS exposure has been shown to be linked to decreased flu vaccine effectiveness. Thus, a study carried out in connection with the C8 studies encompassed 411 adults, whose serum samples were analyzed before and about three weeks after flu (A/H3N2) vaccination [97]. Thus, the elevated serum-PFOA concentrations were associated with a weakened vaccine antibody response also in adults.

e. PFAS exposure has also been shown to be linked to decreased effectiveness of boosters of vaccines first received in childhood. In our study of 12 healthy adult volunteers, increased PFAS exposure was associated with flatter changes in the serum concentrations of tetanus and diphtheria antibodies. Following the booster vaccination, antibody responses widely differed during the first 10 days, with two subjects appearing not to respond at all, and the steepness of the antibody concentration increase was inversely associated with the concomitant serum PFAS concentrations [98].

f. Other studies have also linked PFAS exposure to adverse impacts on the body's ability to fight off various common diseases including colds, fevers and gastroenteritis. Thus, a study of 359 Danish children from the Odense Child Cohort found that increased maternal serum concentrations of PFOA and PFOS at the end of the first trimester was significantly associated with a higher frequency of fever and symptoms in their children. The study followed the cohort of 359 children at ages 1-3 years by monitoring the frequency of fever and associated symptoms every 2 weeks for a year (via text messages). The number of days with fever >38.5ºC (>101.3ºF), and also in combination with nasal discharge or cough, was significantly increased in association with increases in the maternal serum concentrations of PFOA and PFOS [99]. These findings are in accordance with the much smaller Norwegian study already mentioned [96].

g. As part of the studies of the Danish National Birth Cohort, maternal early pregnancy serum from randomly selected 1400 women and their offspring were analyzed by 3M for PFOS and PFOA [100]. Hospitalizations for infection of the offspring were identified by the linkage to the National Hospital Discharge Register, through to age 11 years. Diagnoses, such as airway infection, appendicitis, middle ear infection were merged, and no clear pattern was observed when results were stratified by child's age at infection. In addition to relying only on exposures during early gestation, a recent study raised doubt about the validity of the chemical analyses [34], thus making this study of limited relevance.

h. A new study adds to the existing evidence that prenatal exposure to PFOS and other PFASs is associated with the frequency of respiratory tract infections during the first 10 years of life [101]. Findings from Japan show a similar tendency in 4-years old children [102], where significant trends were seen for both PFPS and PFHxS. These findings strengthen the already existing evidence for PFAS immunotoxicity and its clinical impact.

i. In adults, a study conducted by the C8 Science Panel based on the health examinations concluded in an interim report that increased PFOA exposure was associated with lower serum concentrations of total IgA, IgE (in females only), though not IgG [55]. Thus, using total and non-specific immunoglobulin concentrations, this study is at least partially supportive of adverse immune effects from PFOA exposure. The result concerning IgG concentrations should be interpreted with some caution because the C8 study examined total IgG immunoglobulins (whereas our study, A.1.a. above, focused on concentrations of specific IgG antibodies directed against vaccine antigens).

j. PFASs also have been found to be linked to certain forms of autoimmune disease, in which the body's immune system attacks its own tissues. This link is demonstrated by two studies conducted by C8 Science Panel epidemiologists, the first being an occupational study of 3,713 workers, whose PFOA exposures were evaluated. Using a ten-year lag, the occurrence of ulcerative colitis and, without a lag, rheumatoid arthritis showed significant associations by greater disease frequencies at elevated PFOA exposures [103]. These results were also reflected by the C8 Panel conclusions, where the C8 Panel stressed a probable link between PFOA exposures and ulcerative colitis.

k. The second study concerned the general population in the Mid-Ohio River Valley, where 151 cases of ulcerous colitis were identified in connection with the medical examinations. With a p value less than 0.0001, higher serum-PFOA concentrations predicted a greater risk of developing the disease [104]. In a recent cross-sectional U.S. study, young ulcerous colitis patients had higher serum concentrations of PFOA than controls and those with Crohn's disease [105]; the serum samples were collected within a year of diagnosis, not before.

l. Similarly, in the C8 Panel's study of the >50,000 residents of the Mid-Ohio River Valley, certain immune function parameters were measured. Specifically, antinuclear antibody (ANA) concentrations in serum were used as a screening parameter for autoimmune disease, such as rheumatoid arthritis. There was an increasing trend with serum-PFOA concentrations. In contrast, the inflammation marker, C-reactive protein, fell with increasing PFOA. In each case the pattern was repeated in the same way for males and females [55].

m. Allergies may also be related to PFAS immunotoxicity, as reported by studies linking PFAS exposure to increased development of allergies in children [106]. First, a study of 244 Taiwanese children found that increased cord-blood concentrations of PFOA and PFOS correlated with elevated cord-blood IgE in boys [107]. The immunoglobulin IgE is usually increased in allergic subjects, but the predictive value of elevated cord-blood IgA in regard to subsequent development of allergy or atopy is limited [108]. Further, a study of 343 Japanese births reported an inverse association between PFAS concentrations and cord serum IgE concentrations [109], thus revealing opposite tendencies in the two studies.

n. Using more reliable clinical data, a study of the Faroese birth cohort born in 1997-2000 included data on allergy and asthma at ages 5 to 13 years [110]. Twenty-two of the 559 children had not been vaccinated against MMR, and among those, higher serum concentrations of the five PFASs at age 5 years (but not prenatally) were associated with increased odds of asthma at ages 5 and 13. However, the associations were reversed among MMR-vaccinated children, suggesting that MMR vaccination might be an effect modifier.

o. To further explore the mechanisms, a study was carried out in Norway to characterize gene expression in cord blood and its association with PFAS concentrations, antibody concentrations, and infectious disease incidence. Several immunomodulatory genes, especially the C17 gene, were linked to all three parameters, and these findings therefore supported a PFAS-linked genetic mechanism underlying both the lowered antibody response and the increased susceptibility to infectious disease [111].

p. Regarding occupational exposures, a study of 3M workers found clear associations between increased PFAS exposure and decreased leukocyte counts, a sign of adverse impact on the human immune system. These immunotoxicity appeared to agree with experimental data, especially those in monkeys. The results were reported by Frank Gilliland, MD, as an outcome of his thesis work at 3M about 1990. In his thesis, Dr. Gilliland concluded: "Total serum fluorine was negatively associated with all peripheral leukocyte counts except PMNs [PolyMorphonuclear Neutrophils] and MONOs [Monocytes], which were positively associated" [112]. Of note, the basophil count at elevated exposures was lower in the adults, while a recent study showed that they were higher in highly-exposed children [113].

The files produced by 3M in a recent trial contain a manuscript entitled "Peripheral Blood Lymphocyte Count in Men Occupationally Exposed to Perfluorooctanoic Acid" [114]. As with 3M's monkey study from 1978 that revealed immunotoxic effects [115], the leukocyte count results were not published, and the recommended immunotoxicology assessment was apparently not conducted. I have previously discussed the likely bias in published articles on occupational PFOA exposure (see section V.A.1).

2. Toxicological evidence

Epidemiological evidence showing an association between PFAS exposure and adverse effects on human immune system functions finds additional support in various toxicological studies of immune system functions. Experimental studies have provided substantial documentation of immunotoxic effects [6, 116, 117]. Immunotoxicity of PFASs has been demonstrated in a wide variety of species and models, as well as *in vitro* in relation to human white blood cells.

a. An early 90-day study was carried out in monkeys in 1978 and demonstrated toxicity effects on the gastrointestinal tract and the reticuloendothelial system (i.e. immune system) [118]. The doses of FC-143 (PFOA) given were 0, 3, 10, 30 and 100 mg/kg/day. All monkeys at the 100 dosage and three out of four at 30 mg/kg/day died; compound-related microscopic lesions were seen in adrenals, bone marrow (hypocellularity), spleen and lymph nodes (atrophy of lymphoid follicles in both), as also highlighted by Dr. Gilliland in his thesis from 1992, where he added: "No follow-up studies of these observations have been reported" [112]. Certain of the findings were summarized in a published review article [119] from 1980. The report on the monkey study was released to the U.S. EPA in 2000.

b. Renewed interest in experimental immunotoxicity of the PFASs began after year 2000, at first focusing on reductions in lymphoid organ weights, lymphoid cell numbers, and *de novo* antibody synthesis [116]. These studies clearly document adverse immune system effects and support the notion of PFAS immunotoxicity [6]. Using a standard

immunological challenge of injecting sheep erythrocytes into PFOS-exposed mice, adverse effects were seen at serum concentrations similar to levels observed in occupational exposure, and serum levels were similar to the highest serum concentrations in people with background PFOS exposure [120], while PFOA immunotoxicity occurred at higher serum concentrations [121]. Other studies have shown PFAS effects on immune measures, such as cytokine expression and signaling related to inflammation and T helper cell responses [116].

c. In regard to response to infections, a study in mice demonstrated that PFOS exposure at levels associated with deficient immune functions showed elevated PFOS concentrations in blood, but also in thymus, spleen, and lungs as well as reduced survival after influenza A infection [122].

d. Further, studies of mice injected with sheep erythrocytes, as a standard test of immune system function, demonstrate deficient immune system responses from PFASs, in parallel to the human studies of vaccine responses. Several rodent studies have applied this experimental model to assess any effects on the antibody response. In a study of PFOS, the lowest-observed-effect level (LOEL) for males was 0.05 mg/kg total dose and 10-fold higher in females (which excrete PFOS more rapidly). Measured serum-PFOS concentrations at these dose levels were 91.5 ± 22.2 ng/g and 666 ± 108 ng/g (mean ± SD), respectively [120]. The concentrations would be almost the same if measure in ng/mL, the unit used for human blood samples. Thus, the serum levels measured in the male mice at the lowest dose applied were similar to the highest concentrations measured in residents in the exposed area. Yet, these levels were associated with significant adverse effects. As no lower doses were applied, the data do not allow consideration to which extent lower concentrations may also be associated with adverse effects in this animal model.

e. Available information on immune system effects from developmental exposure also supports a link between PFAS exposure and adverse immune system effects. In one study of gestational exposure, male pups were again more sensitive than females to the effects of PFOS and confirmed that the developing immune system is vulnerable to PFAS exposures and that functional deficits in innate and humoral immunity are detectable at adult age [123].

f. Human white blood cells provide a meaningful *in vitro* model to assess immune system effects, and studies have been carried out to determine the *in vitro* effects of PFAS exposure, generally with a focus on cytokine secretion [116]. White blood cells from human volunteers showed effects at PFOS concentrations of 0.1 µg/mL (or 100 ng/mL) [124], i.e., similar not only to concentrations seen both in affected male mice in toxicology studies, [120] but also to levels in residents highly exposed to contaminated drinking water [125].

3. Perspective

a. In connection with the need to identify a health advisory for contamination of drinking water with PFOS and PFOA, the EPA surveyed the PFAS literature and summarized its results in PFOA and PFOS risk assessment reports [56, 126]. The EPA draft risk assessment documents finds that PFASs exhibit immunotoxicity in experimental models and that the epidemiological evidence is additive, although mixed exposures complicate the attribution of

effects to specific PFASs. A similar conclusion was reached in ATSDR's updated ToxProfile that was recently released [5].

b. In 2016, the NTP reviewed the immunotoxicity information on PFOS and PFOA and concluded that both are "presumed" to constitute immune hazards to humans [6]. Both PFASs suppress the antibody response in animal studies, with a "moderate" level of evidence from studies in humans. The evidence indicating that PFOA and PFOS affects multiple aspects of the immune system supports the overall conclusion that both can be presumed to alter immune function in humans, even though the mechanisms are not clearly understood. The reason for considering the human evidence "moderate" is that all studies are observational (not experimental) and refer to mixed exposures, where the individual and joint roles of PFOS and PFOA are difficult to extract. The term "presumed" is the strongest below "known" in the NTP vernacular.

c. The European Food Safety Authority (EFSA) likewise in their initial opinion in 2008 [1], to which I contributed, relied on experimental toxicity studies at a time where little information on immunotoxicity and few human studies was available. An updated version considered immunotoxicity as one of the major effects in animal studies of PFOA exposure, as also reflected in epidemiological studies [28].

d. According to the recent evaluations, the epidemiological evidence demonstrating an association between exposure to PFOA and other PFASs and adverse effects on the human immune system is strong and is supported by ample toxicological evidence on effects of PFOA and PFOS, while other PFASs have been addressed only in few studies.

e. Species differences must be considered. In agreement with the very detailed NTP review [6], we find that the species differences in PFAS elimination or in immune system vulnerability do not question our conclusions that elevated PFAS exposure presents a human immunotoxicity risk [95, 127]. Thus, also in agreement with the NTP review [6], I conclude that the human evidence strongly supports the existence of PFAS-dependent immunotoxicity at background exposure levels. However, detailed statistical calculations show that PFOA-related effects on specific antibody concentrations appear to be independent of other PFAS exposures [90].

In a medical screening or monitoring program, immune system competency can be assessed by measuring specific antibodies in serum to reveal the response to vaccinations. Insufficient antibody protection can be normalized by a repeat vaccine booster, although that does not improve the protection against other antigens. Screening for immune system deficits can be carried out in newborns [128]. Among other outcomes, such as allergy, the IgE concentration (total or antigen-specific) in serum is routinely used for diagnostic purposes and to identify the correct therapy [129]. Autoimmune diseases like ulcerative colitis, can also be diagnosed and monitored by a survey questionaire, which may assist in treatment choices at early stages [130]. Thus, medical monitoring for the defined population is reasonably necessary and will result in benefits due to early diagnosis, which may be followed by medical intervention.

B. Reproductive toxicity

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that elevated PFOA exposures like those suffered by members of the Bennington Exposure Class result in an increased risk of harm to human reproductive system functions, including pregnancy related conditions, with risks of adverse effects to the next generation. Also in this case, my assessment agrees with Dr. Ducatman's.

The focus in this part is primarily on obstetrical appearances of PFAS toxicity, including pregnancy hypertension and preeclampsia, which conditions were determined by the C8 Panel to have a probable link to C8 exposure [102]. I also address pregnancy outcomes, including miscarriage, birth weight, decreased sperm quality and fecundity. These outcomes may or may not be mediated by endocrine disruption mechanisms, but are dealt with here, as they refer to pregnancy and pregnancy outcomes. Taken as a whole, PFAS exposure at levels similar to or below those reported from Bennington, VT, are associated with a range of reproductive toxicity effects.

Other outcomes considered more clearly to reflect endocrine disruption are considered in the following part and include changes in serum concentrations of sex hormones, delayed development including delayed puberty, inhibited lactation and shorter breastfeeding durations, early menopause, and changes in reproductive hormone concentrations in serum.

Regarding developmental toxicity affecting the next generation functionally and in regard to subsequent disease risks, i.e., so-called Developmental Origins of Health and Disease (DOHaD), these aspects are properly discussed in regard to the relevant organ systems (such as the immune system) [103].

1. Epidemiological evidence

Data from my review of available epidemiological studies demonstrate a strong link between PFAS exposure and adverse effects on human reproductive system functions. One early and important aspect of reproduction is fecundity, i.e., the capability of achieving pregnancy, and other endpoints are then discussed in proper sequence.

Fecundity

As a parameter commonly used in epidemiological studies, time-to-pregnancy (TTP) is a measure of couple fecundity. However, both female and male risk factors must be taken into regard, and studies in this vary in regard to the validity of data collected [131].

a. TTP was obtained in a Danish study of 1240 women, who had achieved pregnancy, thus excluding infertility. The subjects with serum-PFOS in the highest quartile had a 26% reduced chance of becoming pregnant within the same cycle month as compared to women in the lowest quartile [132].

b. A recent Canadian study of over 1,700 women demonstrated that increasing concentrations of PFASs in serum were associated with both reduced fecundability, as measured by increased time to pregnancy, and infertility [133]. Specifically, an increase in one standard deviation in the serum-PFOA concentration was associated with a 31% increase in the odds of infertility and an 11% reduction in fecundability.

c. When my colleagues and I examined PFAS exposures in a prospective study of 222 Danish first-time pregnancy-planners without previous reproductive experience (129 attained pregnancy within 6 months), we calculated the fecundability ratio (FR) using discrete-time survival models [134]. The results showed little, if any, difference associated with serum-PFAS concentrations, although the study may have been too small to reveal an effect.

d. None of these studies involved cohorts with significantly elevated exposures, such as workers in PFAS manufacturing plants or residents of contaminated areas. Still, the available evidence suggests that background exposures to some PFASs affect TTP to a limited extent, as suggested by a Norwegian study [135].

e. None of the recent epidemiological studies used sophisticated technologies that have become available in more recent years. In fact, the waiting-time-to-pregnancy (or time required to conceive) measure relies on a simple questionnaire that has been in use since the 1980s [136]. It is therefore unfortunate that no studies have been located from major PFAS producers regarding fecundity of exposed employees.

Puberty development, irregular cycles, and menopause

f. A cross-sectional study of PFOA and PFOS regarding indicators of sexual maturation was carried out in the Mid-Ohio River Valley. Participants were 3076 boys and 2931 girls aged up to 18 years. They were classified as having reached puberty based on either hormone levels (total >50 ng/dL and free >5 pg/mL testosterone in boys, and estradiol >20 pg/mL in girls) or onset of menarche. For boys, there was a relationship of reduced odds of reaching puberty with increasing PFOS (delay of 190 days between the highest and lowest quartile). For girls, higher concentrations of PFOA or PFOS were associated with reduced odds of postmenarche (130 and 138 days of delay, respectively) [137]. This study may well have underestimated the effects, as it was based on current serum-PFAS values only, although cross-sectional studies on menarche may be biased by PFAS elimination in blood.

g. A more recent study focused on 2,292 children aged 6-9 years who had been examined in 2005-2006 in regard to their exposure to PFOA in the Upper Ohio River Valley [138]. In boys, a higher serum-PFOA concentration was linked to lower testosterone, and PFOS with lower estradiol, testosterone and insulin-like growth factor (IFG-1); in girls, a higher PFOS was associated with decreases in both testosterone and IGF-1.

h. In regard to puberty development, a British birth cohort at background levels found that PFOA concentrations in stored maternal pregnancy serum were slightly higher for 218 daughters who had reached menarche before age 11.5 years compared to a similar number of controls with later onset [139]. The results in this study, however, were not statistically significant.

i. In a Danish study of prenatal exposures judged from maternal serum analysis, 367 daughters' menarche was significantly delayed at higher prenatal PFOA exposures [140]. An important strength is that this study focused on prenatal exposure, although with no adjustment for postnatal exposure from breastfeeding and other sources.

j. In 950 pre-pregnant women, higher serum concentrations of PFOA, PFOS, PFNA, and PFHxS showed increased odds of self-reported history of irregular menstrual cycle and long menstrual cycle [141], i.e., disruptions that may be related to an increased risk of subfecundity [142].

k. The C8 Health Project examined 25,957 women aged 18–65 years regarding serum estradiol concentrations and onset of menopause [143]. The odds of having experienced menopause increased significantly at higher exposures to PFOA and PFOS within the subgroup of middle-aged women. Again, PFAS elimination in blood may have affected the results.

Semen quality

l. A joint analysis of data from three countries suggested a substantially lower proportion of morphologically normal sperm cells at increased serum concentrations of PFOS and PFHxS, while a small increase (opposite direction) appeared to be related to PFOA exposure [144]. Effects on reproductive hormones were also measured and are dealt with separately below. I note that the study design was less than optimal.

m. In a study of 256 men examined at a fertility clinic, no association between the current serum concentrations of PFOA and PFOS and semen parameters was found [145]. However, the concomitant concentrations may not reflect the exposures at the most vulnerable developmental stage or stages where negative effects on semen formation may have happened.

n. In 105 young Danish men from the general population, those with elevated combined serum concentrations of PFOS and PFOA had a median sperm count that was 2.5-fold lower than the median for men with low PFOS–PFOA exposures [146]. Other associations were not statistically significant, but suggested altered pituitary–gonadal hormones at higher exposures to PFOS and PFOA.

o. From a pregnancy cohort established in Denmark in 1988-1989, about one-third of the men (169) was recruited at age 20 years to obtain a semen sample and a blood sample [147]. PFOA and PFOS were measured in banked maternal pregnancy serum samples. In utero PFOA exposure was associated with lower sperm concentrations and sperm counts, while PFOS did not appear to be associated with any of these outcomes. The study design aimed at exploring developmental effects rather than impact of concurrent exposures.

p. According to a recent review, a total of sixteen studies have explored the association between PFAS exposure in men and semen parameters, reproductive hormone levels, or TTP. Despite somewhat inconsistent results, subtle associations between higher PFOS and lower testosterone or abnormal semen morphology have been found in some of the studies and cannot be ignored. Also, eleven studies assessed the association between PFAS exposure in women and Time To Pregnancy (TTP), as a measure of fecundity, or reproductive hormones levels. Four of eight studies found prolonged TTP with higher PFOS or PFOA, while one of the four found an association when restricting to nulliparous women [148]. Again, a concern is the

time of blood collection for exposure assessment, as adverse effects could be due to, say, pre-puberty exposures. Even considering publication bias, the evidence is highly suggestive.

Miscarriage

q. Available evidence suggests that miscarriage and stillbirth are associated with PFAS exposure, although the evidence is not yet strong. This is perhaps not surprising as miscarriage and stillbirth, like mortality, are extreme outcomes. A recent study that included more than 300 miscarriages found a tendency towards a positive association with PFOS exposure in the Mid-Ohio River Valley, but no association between PFOA exposure and miscarriage [149].

r. A subsequent Danish case-control study of 51 miscarriages utilized serum collected in first trimester and found a significantly increased risk associated with C9 and C10, and a tendency in the same direction for PFHxS, but no clear association for PFOA and PFOS [150]. This study likely had too low a statistical power to reveal minor adverse impacts.

Pre-eclampsia and higher blood pressure during pregnancy

s. The C8 Science Panel concluded that PFOA exposure is associated with reproductive toxicity, i.e., an increased risk of pre-eclampsia and higher blood pressure during pregnancy [151]. This conclusion rests on extensive studies in the contaminated Upper Ohio River Valley. Data were obtained on 1,845 pregnancies within the 5 years preceding the serum-PFOA analysis and on 5,262 pregnancies analyzed for PFOS. Preeclampsia was weakly associated with PFOA and PFOS [152].

t. However, a more recent study is less convincing. Relying on the serum-PFAS analyses from the health examinations in 2005 and 2006, birth records from singleton pregnancies were obtained to identify the 106 cases of pregnancy-induced hypertension. Serum PFOA and PFOS were both positively associated with the diagnosis [153].

u. Using data from the Norwegian Mother and Child Cohort Study, a study was conducted of 976 nulliparous pregnant women, of whom 466 had a validated diagnosis of preeclampsia. No strongly positive associations between PFAS levels and preeclampsia in this population with low background exposures [154]. Thus, the conclusion today is less clear than it was when the C8 Panel based its conclusions solely on the findings in the highly contaminated communities. However, the evidence does not speak against the wisdom of monitoring for preeclampsia and hypertension in pregnancy.

v. In its survey in Bennington, the VT Department of Health found that a history of preeclamposia was associated with an elevated serum-PFOA concentration.[s]

[s] Vermont Department of Health. Exposure to Perfluorooctanoic Acid (PFOA) in Bennington and North Bennington, Vermont: Results of Blood Testing and Exposure Assessment, September 2017.

Preterm birth and low birth weight

w. The C8 Science Panel also evaluated the evidence on preterm birth, birth weight and fetal growth. Some studies available by then suggested small negative shifts at high PFOA exposures [155, 156], but the Panel considered them uncertain and therefore insufficient to conclude the presence of a probable link. EPA in its most recent evaluation considered decreased birth weight in rats one of the critical outcomes for PFOS [126]. A meta-analysis of nine epidemiological studies showed a highly significant, though fairly small, decrease in birth weight at elevated PFOA exposure [157]. By now, this outcome is also considered as an established hazard by ATSDR [5] and EFSA [28].

x. Relating to the C8 studies, women who reported reproductive histories and who provided serum for the C8 study at the examinations were linked to data on preterm birth and birth weight. Elevated serum concentrations of PFOA and PFOS at the health examination in 2005-2006 were associated with a greater frequency of lower birth weight at term [153].

y. A study in Denmark demonstrated increased birth weight in girls at higher exposures to PFOS, PFOA, and PFHxS and reduced birth weight in boys, thereby suggesting possible sex-dimorphic effects [158]. In support of this notion, the same study also measured the anogenital distance in 511 children and observed decreases in girls, though not in boys, at elevated maternal PFAS exposures. In a recent study, birth weight in Norway was apparently not affected by background levels of PFAS exposures [159]. The most recent report from the Japanese Hokkaido cohort shows that low background exposures to PFOS and PFOA are associated with decreases in birth weight, and the study also highlights that hormones such as leptin and adiponectin may play a role [160].

z. A British study of the ALSPAC birth cohort collected serial data on weight and height up to age 20 months and showed that elevated maternal serum concentrations of PFOS, PFOA and PFHxS were associated with decreased birth weights in girls but that higher PFOS exposures were then associated with increased body weight at 20 months [161].

aa. A similar study from the Faroes revealed that a higher maternal pregnancy serum-PFOS concentration was associated with increased weight (and overweight) in the child at age 18 months, while PFOA rather showed a similar association with weight at 5 years of age [162]. These findings suggest that birth weight as an outcome at a particular point in time may need to be seen as part of an intrauterine-postnatal growth profile.

2. Toxicological evidence

A significant part of the early toxicological evidence concerning reproductive harm from PFASs comes from industry-supported studies. Extensive information is available from recent reviews [5, 7, 56]. Although outcomes applied in experimental studies often do not overlap with those used in human studies, there is general agreement between these two sets of evidence.

3. Perspective

The C8 Science Panel did not conclude that there is a probable link between exposure to PFOA and birth defects [163], but other reproductive adverse effects are more likely. A link to pre-eclampsia was considered sufficiently justified by the Panel [151], but support for this link remains limited. At that time, a link to decreased birth weight was not reported, but growing evidence suggests that decreased fetal growth regards time-dependent postnatal growth patterns.

The C8 Panel did not look as broadly at reproductive and related developmental issues as I have, given the findings that could be made based on the feasible methodologies and population groups available at the time. Recent evidence is highly suggestive of adverse effects on female reproduction, as indicated by increased occurrence of abnormal puberty development, irregular menstrual cycles and decreased fecundity. Male toxicity is also much better documented now, although in both cases, exposure misclassification needs to be carefully considered, as I have done above. In deciding on a provisional weekly tolerable intake (PTWI), EFSA considered decreased birth weight one of the major adverse effects of PFOA exposure [28].

Therefore, based on the weight of all the evidence, it is my opinion that elevated exposure to PFOA results in an increased risk of harm to human reproductive system functions.

C. Endocrine disruption

Outcomes usually considered to reflect endocrine disruption will be dealt with in the present part, including changes in reproductive hormone concentrations in serum and inhibited lactation as indicated by shorter breastfeeding durations in exposed women. My conclusions are in agreement with Dr. Ducatman's.

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that elevated PFOA exposures like those suffered by members of the Bennington Exposure Class result in an increased risk of harm to human endocrine functions, including an increased risk of thyroid disease and shorter durations of breastfeeding in pregnant women.

Based on the available evidence, the thyroid gland is a target organ for PFOA toxicity, as supported by laboratory experimental data [164] and recognized by the C8 Panel [165]. The Panel report is quite comprehensive, and the coverage of thyroid dysfunction will therefore emphasize major and recent studies. Even subclinical hypothyroidism is a health concern, especially during pregnancy, as fetal brain development is highly vulnerable to deficiency in maternal thyroid hormone supplies [166, 167]. Moreover, as the thyroid gland is the target for a substantial number of environmental chemicals, PFOA and other PFASs are likely to contribute to joint effects in combination with exposures to other thyroid toxicants [168]. Thyroid dysfunction can be identified at early stages by blood tests that may trigger appropriate treatment, e.g., with thyroid hormone supplements. ATSDR concludes that increased risk of thyroid disease is an effect of PFOA exposure [5].

Based on the weight of the epidemiological evidence and supporting toxicity evidence, I conclude that PFOA exposure result in an increased risk of harm to human health regarding increased risks of developing diabetes and metabolic disease or dysfunction. These outcomes include an increased risk of developing overweight or obesity. As these conditions are common and increasing in prevalence, even a small increase in diabetes risk and obesity would be of major public health impact [169, 170].

Although the C8 Science Panel concluded that the evidence available to them at the time was insufficient to conclude that PFOA is linked to the development of type 2 diabetes (T2D) [171], recent evidence strongly suggests that PFAS exposure has a potential of causing adverse metabolic effects, including the development of T2D and obesity, as part of current exposures to so-called obesogenic chemicals [172], especially in regard to developmental exposures [173]. The recent prospective evidence on these outcome was published after the deadline for recent risk assessments.

Endocrine disruption effects are generally defined as adverse effects in an intact organism or its progeny that have an endocrine mode of action, i.e., that it alters the function(s) of the endocrine system. Due to the serious human health consequences, endocrine disruption has become a top priority in chemicals control efforts in the EU and elsewhere [174].

Based on the available evidence, PFASs are convincingly associated with endocrine disrupting effects that may have substantial adverse impacts on the exposed populations. While endocrine disruption is often thought to be related to reproductive toxicity, a wide variety of hormones play a role for various physiological functions, and their disruption can cause a variety of dysfunctions and diseases. Hormones addressed by PFAS research include sex hormones, thyroxin, and insulin. Diagnostic procedures can be used for medical monitoring purposes to identify exposed subjects that may require hormone supplements or other intervention.

1. Epidemiological evidence

Serum-hormone concentrations

a. Early evidence on endocrine disruption associated with PFAS exposure originates from a doctoral thesis project, where Frank Gilliland, MD, studied clinical pathology parameters in 111 male workers in 3M's Chemolite plant in Cottage Grove, MN [112]. There was a positive correlation between PFOA exposure measured as serum TOF and estradiol (an adverse effect), and a negative correlation with free testosterone (also an adverse effect) with this association being stronger in older men. Dr. Gilliland therefore concluded that PFOA may affect male reproductive hormones [112]. This finding is in accordance with the evidence on reproductive toxicity in males as summarized in Section VIII.B.1. However, this study was not reported on its own in a scientific journal, but was referenced in a subsequent article led by 3M authors [175].

b. This subsequent follow-up study further explored serum hormone abnormalities in exposed workers and likewise showed a positive correlation between PFOA exposure and serum-estradiol (an adverse effect) [175] in 111 and 80 production workers studied

in 1993 and 1995. The 10% increase in mean estradiol levels observed among those employees with the highest serum-PFOA concentration was argued to be potentially confounded by body mass index (although the risk of obesity may be increased at higher PFAS exposures, see section VIII.E). Even though two sets of data were available, and 68 participated in both (and some likely were also examined by Dr. Gilliland), the authors chose not to conduct comparisons over time, allegedly due to variability of the hormone analyses. The 3M authors concluded that the results provided reasonable assurance that, in this production setting, and contrary to the directionality of Dr. Gilliland's findings [112], the authors reported no significant hormonal changes associated with PFOA at the serum levels measured. In my mind, the statistical analysis of the data is incomplete, and the conclusions drawn may not be appropriate.

c. The C8 Health Project examined 25,957 women aged 18–65 years regarding serum estradiol concentrations [143]. There was a significant inverse association between PFOS and estradiol, though not between PFOA and estradiol, thereby suggesting that endocrine effects from PFAS exposure may differ between men and women. As mentioned in section B, there was also an increased odds of having experienced menopause at elevated exposures to PFOA and PFOS among study participants.

d. In a study of nearly 2,300 children living near a PFOA production facility in the Mid-Ohio River Valley, increased PFAS exposure correlated with lower levels of sex hormones. Especially in boys, increased PFOS concentrations were associated with lower testosterone, estradiol, and IGF-1 levels, and increased PFOA concentrations were correlated with lower testosterone levels. In girls, increased PFOS concentrations were associated with lower testosterone and IFG-1 levels [138]. Again, this study supports the notion that the PFASs are endocrine disruptors and that sex-related effects may differ by age.

e. A study of postpubertal women at age 15 years whose mothers were exposed to PFASs at background levels in the UK found that higher levels of maternal exposure to PFOS, PFOA, and PFHxS were correlated with higher testosterone concentrations. Findings from this study suggest that prenatal exposure to PFASs leads to adverse effects that may be lasting and may be expressed during or after puberty [176]. Again, differential effects may be observed in regard to different developmental stages.

f. A study of 540-person cohort in Taiwan found that increased serum concentrations of PFOA and PFOS were correlated with decreased levels of sex hormones in adolescents and young adults at ages 12-30 years [177]. PFOS was associated with a significant decrease in follicle-stimulating hormone (FSH) levels in young men aged 12-17, and in serum testosterone levels in young women of the same age. PFOA was associated with a significant decrease in serum levels of sex-hormone binding globulin (SHBG) in the young women aged 12-17 years, and negative associations between PFAS exposures and the hormones measured were particularly strong in the young women

g. From the Danish pregnancy cohort established in 1988-1989, the 169 men at age 20 showed higher adjusted levels of luteinizing hormone (LH) and FSH associated with higher prenatal PFOA exposures [147]. PFOS did not appear to be associated with hormone concentrations.

h. In 105 young Danish men at background exposures, hormone profiles suggested poorer function of Leydig cells (which produce testosterone) at higher PFAS exposures. However, the associations in this small study were not statistically significant [146].

Duration of breastfeeding

i. A study of 1,400 Danish women reported that the duration of breastfeeding, as recorded by two telephone interviews, decreased at increasing serum-concentrations of PFOA and PFOS, although only in multiparous women [178]. In multiparous women, previous breastfeeding might confound the association, and this finding therefore did not provide strong support for a causal association.

j. A recent study in the U.S. [179], however, found that increased maternal serum-PFOA concentrations were correlated with a decreased duration of breastfeeding, and that this association was not confined to multiparous women and is independent of potential confounders, thereby supporting a hypothesis of endocrine disrupting effects. Although the recording of duration of exclusive breastfeeding may have been somewhat imprecise, the fact that the women were not aware of their own exposure levels excludes any important bias.

k. These findings are supported by a subsequent study of 1,130 new mothers in the Faroe Islands [180]. A doubling of maternal serum PFAS concentrations was associated with a reduction in duration of both total and exclusive breastfeeding, most pronounced for PFOS, where a doubling was associated with a reduction in total breastfeeding of about six weeks. Similar effects were seen for PFOA, though not for PFHxS. These associations were evident among both primiparous and multiparous women, and thus cannot be explained by confounding from previous breastfeeding. Similar results from a Danish mother-child have recently been reported at a scientific conference, again highly significant (Timmermann et al., submitted).

Thyroid hormones and related diseases

l. Dr. Gilliland analyzed in his doctoral thesis data from his cross-sectional study of 3M production plant workers regarding thyroid effects associated with organofluorine concentrations in serum. A positive correlation was seen between organic fluorine and the thyroid stimulating hormone (TSH) in serum [112]. Elevated TSH is often seen when thyroid functions are deficient. In a later paper on thyroid function measurements in about 500 workers from 3M production plants in Alabama and Belgium, 3M scientists argued that variable associations with thyroid hormones (and all other clinical pathology parameters measured in this study) were of limited, if any, clinical relevance [57]. Again, this industry study does not seem to present the necessary data to justify the conclusions.

m. A cross-sectional data set from the C8 Health Project on 52,296 adults with a year or more of exposure to contaminated drinking water showed that both PFOA and PFOS in serum were associated with significant elevations in serum thyroxine (T4) and a significant reduction in triiodothyronine (T3) uptake in all participants, thus showing disruption of thyroid functions [181].

n. A later study of 33,254 exposed community members and production workers applied calculated temporal trends in serum-PFOA concentrations [182]. The occurrence of 2,109 cases of functional thyroid disease, i.e., hyperthyroidism and hypothyroidism, was associated with PFOA exposure in women, while exposed men showed a tendency of hypothyroidism at elevated exposures.

o. In 10,725 children and adolescents aged 1-17 years examined within the C8 community study, a tendency was seen toward an increased risk of an increased serum concentration of total T4 concentrations was found for PFOS, but was not significant for PFOA. Further, an increased OR for hypothyroidism (observed in 39 cases) was found at the highest quartile of PFOA exposure [183].

p. In a study based on data from the National Health and Nutrition Examination Survey (NHANES) on 3,974 adults, serum concentrations of PFOA and PFOS were compared between subjects with and without self-reported thyroid disease [184]. Women with a serum-PFOA concentration in the highest quartile were more than twice as likely to report current treated thyroid disease compared to women with low PFOA levels. The same tendency was seen in men, although it was of borderline significance. For PFOS, the trend was significant in men, but not in women. Although the exposure was apparently measured after the diagnosis, the association appears plausible and may well occur at background exposure levels.

q. In a similar NHANES-base study of 1,181 adults, higher serum concentrations of PFOA were associated with increased serum concentrations of T3, while PFHxS was linked to increases in both T3 and T4, but to lower T4 in men [185]. These findings suggest sex-dimorphic effects of PFASs on thyroid functions.

r. A recent study of a birth cohort in Boston supports the notion that current PFAS exposures may influence thyroid functions in the mother and in the baby [186].

Diabetes

s. The C8 Science Panel did not find any indication that PFOA exposure was related to diabetes mortality [182] [171]. However, fasting serum insulin decreased at higher PFOA exposures [187], thus suggesting possible pathogenetic impact.

t. Additional support for background PFAS exposure being a risk factor for T2D comes from certain cross-sectional studies such as the NHANES data [188, 189]. Given that the data are cross-sectional, they may likely underestimate the true diabetogenic impact of PFAS exposure.

u. In a study in Taiwan, serum-PFOA in adults was positively correlated (adverse effect) with their beta cell function (possibly as a sign of compensation for insulin resistance), and PFOS was positively correlated (adverse effect) with blood insulin, insulin resistance (homeostasis model assessment), and beta cell function [188].

v. Data on 499 prepubertal children [190] showed that current exposures to PFASs are linked to increased risk of overweight and deficient glucose homeostasis. In 811

children from the Danish national birth cohort, prenatal exposure to PFOA and PFOS did not seem to be associated with height and weight at age 7 [191], but the validity of the PFAS measurements has later been called into doubt [34].

w. Strong evidence was recently contributed from the Nurses' Health Study II participants who had provided blood samples in the late 1990s [192]. Among those who were free of diabetes, cardiovascular disease, and cancer at the time, we identified and ascertained 793 incident T2D cases through 2011 (while ignoring the first year after blood collection). Matched diabetes-free controls were selected. After multivariate adjustment for T2D risk factors, higher plasma concentrations of PFOS and PFOA were significantly associated with an elevated risk of developing T2D. Comparing extreme tertiles of PFOS or PFOA, the ORs; 95% CIs were 1.61 (1.08, 2.39; P_{trend}=0.03) and 1.53 (1.04, 2.26; P_{trend}=0.03), respectively. Other PFASs were not significantly associated with T2D risk. These findings from this prospective study are particularly important because the nurses had background exposures only.

2. Toxicological evidence

Endocrine disruption effects in humans are supported by a substantial number of experimental animal studies [4, 8, 10, 56, 126]. A few key studies are highlighted below.

a. An early study of the effects of APFO (the ammonium salt of PFOA) exposure in rats showed a substantial increase in hepatic aromatase activity [193]. An increase in aromatase activity is likely to increase the formation of estradiol from testosterone, thus a decrease in serum-testosterone and increase in estradiol. Accordingly, changes in serum concentrations of testosterone and estradiol are considered likely to be due to PFAS-mediated changes in the hepatic aromatase activity [194], but interference with sex hormone receptors has also been reported [195]. Such modes of action could well mediate the PFAS-associated endocrine disruption findings in epidemiology studies.

b. A recent study examined the effect of PFOA and PFOS exposure on proteins and cells related to the male reproductive system and demonstrated that both PFOA and PFOS inhibit important drug transporting proteins present in the blood-testis barrier, thereby potentially contributing to male infertility [196].

c. Endocrine disruption effects appear to be independent of peroxisome proliferator activated receptor (PPAR) activation and therefore are likely relevant to human PFOA toxicity [8]. Among reported mechanisms, PFOA can activate nuclear receptors other than PPAR, i.e., the constitutive androstane receptor (CAS) and the pregnane X receptor (PXR), and activation of the estrogen receptor (ER) may also be involved [197, 198]. Local testicular effects are indicated by induction of Leydig cell hyperplasia and adenoma in experimental studies, apparently independent of PPAR activation [117].

d. Experimental studies show that mammary gland development in mice is inhibited by PFOA exposure during early development at serum concentrations similar to those occurring in residents in Bennington [8, 10, 199, 200]. The State of New Jersey regards this as one of the most sensitive non-carcinogenic endpoints in rodents [201] (see section IX).

e. Thyroid dysfunction in humans exposed to PFASs is supported by a wide range of studies in laboratory animals [4], and the sensitivity of thyroid functions to environmental chemicals is well documented [202]. Most of the evidence regards PFOA and PFOS, with some studies also covering PFHxS and longer-chain PFASs.

f. Reviews of experimental evidence on obesogenic and diabetogenic chemicals cover the evidence in PFASs as causes of diabetes development [172, 203], also regarding developmental exposures [173]. Rodent studies have demonstrated that glucose homeostasis is adversely affected by PFAS exposure [204].

3. Perspective

a. Regarding endocrine disruption, substantial research activity has emerged during recent years, and much improved toxicological understanding of the mechanisms involved has resulted. In addition, a wealth of epidemiological studies has documented the adverse human health consequences [174].

b. As mentioned under C.1.b, the paper co-authored by 3M scientists and Dr. Gilliland in 1998 reported on clinical pathology results from serum analyses, including reproductive hormones and concluded that there were no significant hormonal changes associated with PFOA at the serum levels measured [205]. While this conclusion was counter to Dr. Gilliland's findings in his thesis project [112], the data analysis in the published paper seems inadequate to justify the conclusion. One difference between the 1998 and Dr. Gilliland's thesis is that Dr. Gilliland relied on total organofluorine concentrations, and the subsequent study referred to PFOA, but this issue was not explored in the published paper. Likewise, the fact that the control group was not unexposed to PFASs was not considered.

c. Serum-hormone changes observed in relation to semen quality suggest that they are both related to endocrine disruption mechanisms, as also indicated by experimental studies in laboratory animals. A concern is that most studies have relied upon PFAS concentrations measured in serum obtained at the wrong time, i.e., not regarding past exposures and the most vulnerable developmental stages. Such exposure misclassification will likely result in an underestimation of the true PFAS effects [206]. Thus, in my opinion, results showing adverse effects could be even stronger during vulnerable developmental time windows is also supported by our studies on prenatal exposure to pesticides [207-209].

d. These findings are of great health relevance, given the known excess mortality associated with decreased serum-testosterone concentrations in men [210]. Thus, medical monitoring of the exposed population for serum-testosterone in men is reasonably necessary to identify early stages of endocrine disruption that may be appropriately treated with testosterone supplements.

e. Recent evidence suggests that thyroid toxicity is of particular relevance in pregnant women with a pre-existing thyroid dysfunction [211]. This issue has not yet been explored regarding PFAS effects, and the evidence so far does not allow any conclusion on impact of PFAS exposure in the presence of borderline iodine deficiency. In general, the lack of assessment of PFAS exposures at the most vulnerable time, lack of assessment of contributing

factors, and other determinants will tend to weaken any true association between PFAS exposure and adverse effects on the thyroid gland.

f. Adverse effects on thyroid functions in pregnant women is relevant also in regard to possible developmental neurotoxicity, as certain hormones are crucial to brain development [212], in particular thyroid hormone [167]. A recent neurotoxicology review suggested that developmental effects due to PFASs may be mediated by thyroid toxicity, influence on calcium homeostasis, protein kinase C, synaptic plasticity and cellular differentiation, perhaps as part of a cocktail of substances that in combination reach harmful concentrations [213]. Given the PFAS-associated hormonal disruptions that may occur during fetal development, neurodevelopmental toxicity is likely. The developing brain is a highly sensitive target for environmental chemicals [214], and available evidence shows that the human brain is also likely to be vulnerable to PFAS toxicity, although assessment of the magnitude of PFAS-associated neurotoxic risks is not yet possible.

g. Only recently has scientific attention focused on developmental neurotoxicity as a highly sensitive outcome that can have serious consequences, also in regard to economic costs to society [201]. While it could have been relevant and appropriate to examine neurotoxicity from prenatal exposures, and while evidence of such effects due to lead contamination were well known already in the 1980s [211], this issue was not explored at the time, and the C8 Panel did not make this a priority, presumably because little evidence at the time suggested that the developing brain could be an important target organ in regard to PFAS exposures. My judgment therefore relies on the coverage and directionality of very recent research and the likelihood that established neurotoxic mechanisms are triggered by PFAS exposure.

h. For the exposed population, monitoring for thyroid function is reasonably necessary and beneficial, as PFAS-associated thyroid dysfunction could be identified early in the pathogenesis and treated with a better prospect for the patient than if the disease was diagnosed at a later stage when symptoms become apparent. Medical monitoring for thyroid function in pregnant women with elevated PFAS exposure would also represent a major contribution to preventing developmental neurotoxicity in children [215].

Much attention is currently being paid to these issues regarding PFAS exposures, in birth cohorts and in prospective studies of adult populations. Future report on such studies are likely to substantially extend the data base to evaluate the endocrine disruption impacts of PFAS exposures.

Recent information suggests that obese persons are healthier and live longer now than in previous decades, likely because of better care and risk-factor management [216]. However, the joint public health effect of increased prevalence and decreased mortality leads to more years spent with obesity and more time for the damaging coexisting illnesses, such as T2D diabetes and chronic kidney disease, to develop. Medical monitoring for the exposed population is reasonably necessary and would allow early detection of early stages of T2D and would allow improved prevention of late-stage adverse effects, such as blindness, peripheral neuropathy, and kidney dysfunction.

About one-quarter of U.S. adults have undiagnosed T2D [217], and the undiagnosed and untreated proportion is likely to be greater in particular groups at risk, such as subjects exposed to diabetogenic substances like PFOA. While recommendations differ, the use of fasting plasma glucose ≥100 mg/dL or hemoglobin A1c ≥5.7% would represent a major public health advantage [218]. Identifying subjects with early or latent stages of this serious disease by periodic diagnostic medical examinations would allow treatment that would be particularly beneficial when the disease is identified early in the course. Medical monitoring of the exposed population for latent stages of endocrine diseases or dysfunctions is reasonably necessary to allow early detection and beneficial intervention.

D. Liver function abnormalities

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that elevated PFOA exposures like those suffered by members of the Bennington Exposure Class result in an increased risk of harm to human liver functions, with related adverse health effects, including the development of non-alcoholic fatty liver disease (NAFLD). Also in this regard, my evaluation agrees with Dr. Ducatman's.

The liver is an important target organ for PFAS toxicity in humans as in animals, and such effects have been referred to by regulatory agencies in regard to determining tolerable exposure limits [1, 4, 56, 126]. Taken as a whole, PFAS exposure at levels similar to or below those reported from the area around the polluting facility are associated with a range of liver toxicity effects.

PFAS's adverse effects on liver functions are reflected by elevations of serum-cholesterol concentrations and other important serum lipid parameters. Even small increases are likely to have negative implications regarding cardiovascular disease and mortality. In this regard, the C8 Panel concluded that PFOA is linked to an increased risk of elevated serum-cholesterol, and but not (yet) hypertension and coronary artery disease [219]. As hypercholesterolemia and cardiovascular disease are of major public health concern, these issues are discussed under a separate heading (Section VIII.E).

1. Epidemiological evidence

a. Increased serum-cholesterol concentrations at elevated PFAS exposures likely relate to toxic effects on liver functions, and increased concentrations of liver enzymes in serum at higher PFOA exposures support this notion in about a dozen epidemiological studies. An early mention of adverse liver effects from PFAS exposure in workers is from 1978, as described in my report to the State of Minnesota.

b. In 1980, DuPont shared the results of a pilot study called "liver enzyme study of workers exposed to perfluorinated octanol compounds (C-8) at Parkersburg," where they found elevated mean serum concentrations of aspartate aminotransferase (AST, previously referred to as SGOT) and alkaline phosphatase (AP) among exposed workers.[t] This report later

[t] AR226-1465.pdf, January 28 1980, Liver Enzyme Study of Workers exposed to C-8 at Parkersburg, Exhibit CC (EID099433-34). Page 000186.

became available from the U.S. EPA (as are all documents identified by a document number beginning with AR226).

c. In his thesis, Dr. Gilliland found increases in serum concentrations of SGOT and SGPT (now referred to as AST and ALT), as well as a tendency toward lower high-density lipoprotein (HDL) cholesterol, as markers of adverse effects on liver function [112]. Other cross-sectional studies [191, 248] were not informative in this regard, perhaps because a variety of other factors can impact on liver functions. The studies were reviewed in greater detail in regard to immune function parameters in Section VIII.A.

d. Further analyses of medical surveillance data on PFOA-exposed workers in Minnesota led to a 3M paper that relied on cross-sectional analyses of PFOA and liver function data collected in 1993, 1995 and 1997 [220]. While the wording differs from a previous report [205], the authors concluded that employees' serum PFOA levels were not positively associated with either clinical hepatic toxicity nor hepatic responses to obesity and alcohol.[u]

e. Dr. Olsen and Professor Mandel reported in 1998 results on PFOS-exposed Antwerp and Decatur male fluorochemicals production workers, in which they concluded that hematological, clinical chemistry and hormonal abnormalities were not associated with serum PFOS levels up to 6 ppm (6,000 ng/mL).[v] Although deviations occurred at higher exposures, the authors disregarded these findings, basing this decision on a determination there were too few subjects to allow a firm conclusion [221]. A later analysis of medical surveillance data from the workers again showed a positive association between the serum-PFOA concentration and both cholesterol and triglycerides. Although incompletely reported, the findings were considered implausible, as they were not in accordance with animal data at much higher exposures [57].

f. However, new information on this study has surfaced at a recent law suit, as internal company documents were released and are now available from the office of the Minnesota Attorney General. Among these documents is a draft, dated October 11, 2001, of the published article.[w] This draft lists the same authors and concludes that there was a positive association between PFOA and serum cholesterol and triglycerides over time, as based on 20 tables with regression results. Only partial results without *p* values from four of the tables were included in the published article [57]. This article has been cited about 200 times in the scientific literature and by regulatory agencies as indication that high levels of occupational PFOA exposures are not hepatotoxic, and the validity must now be called in doubt.

g. The C8 Health Project examined 47,092 adults for effects of PFOA and PFOS on alanine transaminase (ALT), gamma-glutamyltransferase (GGT), and bilirubin as

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[u] AR226-0477. Geary W. Olsen, et al., An Epidemiologic Investigation of Plasma Cholecystokinin and Hepatic Function in Perfluorooctanoic Acid Production Workers, 3M Final Report EPI-0003 (1997), with Summary of study, Protocol, and Manuscript accepted for publication in 2000, Drug & Chemical Toxicology. Page 003511.

[v] AR226-0030. An Epidemiologic Investigation of Clinical Chemistries, Hematology and Hormones in Relation to Serum Levels of Perfluorooctane Sulfonate in Male Fluorochemical Production Employees (List of Section Attachments is first page of this File). Page 001074.

[w] Draft manuscript dated October 11, 2001, PTX1799, Bates pages 3M-MN02482163-225. Available from https://www.ag.state.mn.us/office/contactus.asp.

markers of liver function. These results showed a positive association between serum PFOA and PFOS concentrations and the serum ALT concentration [222], usually interpreted as a sign of hepatocellular damage. When serum-PFOA concentrations were modeled as cumulated concentrations, the adverse effect on serum ALT concentrations was replicated in a mixed Ohio River Valley population [223].

h. Likewise, in a general population sample from the NHANES study, liver enzymes showed significant, though small, increases at higher serum-PFOA concentrations [224].

i. Several occupational studies, both cross-sectional and prospective, have assessed liver function parameters in serum, the most recent ones [220, 225, 226] showing that, in general, liver enzymes tend to increase, while bilirubin decreases at higher PFAS exposure levels.

2. Toxicological evidence

a. The liver was early identified as a main target organ in rodents [119]. Although toxic mechanisms may differ between rodents and humans [8, 117], as I discussed above, the PPAR-related mechanism is no longer believed to be the differentiator that 3M once made it out to be [11].

b. Detailed discussion of liver toxicity in experimental models is included in recent evaluations by regulatory agencies [4, 56, 126], to which little recent evidence adds only little.

c. One aspect deserves consideration, i.e., the intrahepatic lipid metabolism. Some PFASs have the potential to induce hepatic lipid accumulation in cynomolgus monkey [227] and induce lipid synthesis gene expression in human hepatocytes [228].

d. In mice, PFOS administration induced hepatic steatosis in time-and dose-dependent manner along with corresponding CD36 and Lpl expression induction and decreased mitochondrial β-oxidation in mice [229]. Also, in exposed animals, accumulation of lipid droplets in hepatocytes was observed. These findings suggest that steatosis and fatty liver degeneration may be relevant outcomes of elevated PFAS exposure.

3. Perspective

Even though the liver and lipid metabolism were identified early on as likely targets of PFAS exposure, it appears that the understanding of the impact on workers' health and on exposed communities in general developed very slowly and that great hesitation was repeatedly voiced against accepting a hypothesis of PFAS hepatotoxicity.

a. As late as 2003, 3M authors argued that a positive association between PFOA exposure and cholesterol in 3M workers "is contrary to the substantial body of toxicological literature that suggests a negative association in laboratory animals" [57]. However, in a more recent article [230], the 3M authors relied on a species difference in liver metabolism (associated with the PPAR receptor) and for this reason concluded that

hepatocellular tumors in rats are "not likely to be relevant to humans." However, these positions are inconsistent. It is not appropriate in one connection to require similar hepatotoxic effects in different species and in another to raise doubt about such similarity. I also note that PFOA metabolism is not affected by cholesterol-lowering medication [60], thus making reverse causation highly unlikely.

b. In regard to liver steatosis, up to 10% of adolescents have NAFLD [231, 232]. As a considerable and apparently growing public health problem of partially unknown origin, this outcome requires attention in future studies of PFAS-associated adverse human health effects.

c. EFSA considered elevations in ALT as one of the major adverse effects of PFOA exposure in adults when deciding on a PTWI [28], even though ALT elevations were mostly considered within the reference range.

d. Clearly, monitoring of liver functions in the exposed population would be reasonably necessary and appropriate to allow early detection of liver related dysfunctions. Much experience is available on the diagnostic use of elevated liver enzyme activities in serum [233], and the high prevalence of NAFLD in the general population supports the need for medical monitoring of liver functions in PFOA-exposed population. Cholesterol is covered below.

E. Cardiovascular disease

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that PFOA exposure results in an increased risk of harm human health due to elevated serum lipids and obesity, both of which are important risk factors for the development of cardiovascular disease. The evidence is strong that PFASs cause adverse cardiovascular effects, including hyperlipidemia.

As discussed above, serum concentrations of total cholesterol and other important serum lipid parameters increase at higher PFAS exposures. Obesity is considered a result of metabolic abnormalities, where T2D is an additional outcome (dealt with under endocrine disruption). Both confer an increased risk of cardiovascular disease. Even a small increase would likely have negative implications regarding cardiovascular morbidity and possibly mortality. The C8 Panel concluded that PFOA is linked to an increased risk of hypertension in pregnancy, elevated serum-cholesterol, and potentially also coronary artery disease, although the latter was not considered sufficiently supported by the evidence available at the time.

Due to the high incidence of cardiovascular disease, even a small increase in life-time risk is of serious health importance. A recent article recommends immediate action to control 'background' exposures to PFOA [234]. My assessment is in agreement with Dr. Ducatman's.

1. Epidemiological evidence

a. The early 3M occupational study by Dr. Gilliland addressed serum chemistry abnormalities in exposed workers [205] and showed an inverse correlation (adverse effect) between organic fluorine compounds (assumed to be mainly PFOA) and HDL

cholesterol. However, the previously mentioned draft by same authors concludes that there was a positive association between PFOA and serum cholesterol and triglycerides over time, as based on 20 tables with regression results.[x]

b. Evidence from cross-sectional and, in particular, prospective studies of workers at other plants also suggested that increased PFOA exposure is associated with higher serum-cholesterol concentrations, often exceeding the reference range [225, 226, 235].

c. Cross-sectional data on 1216 subjects from the 1999-2003 NHANES showed that increasing serum-PFOA concentrations were positively associated with self-reported cardiovascular disease, including coronary heart disease and stroke, and objectively measured peripheral arterial disease (an ankle-brachial blood pressure index of less than 0.9). The highest PFOA quartile showed a doubling of cardiovascular disease after confounder adjustment [236].

d. Community and general population groups with lower levels of PFOA exposure have also revealed positive correlations (adverse effects) between PFOA and cholesterol concentrations in serum [59, 60, 237, 238].

e. In some populations, other PFASs were also measured, and positive associations were found in regard to PFOS exposure [59, 60, 238], a finding that we have replicated in elderly subjects from the Faroe Islands, where exposure levels are similar to background levels in the US (unpublished results).

f. Data from the C8 project showed that total cholesterol and low-density lipoprotein (LDL) -cholesterol increased at higher PFOA exposures (and HDL increases in women) [187]. The variability in PFAS-associated cholesterol changes is quite large [9], possibly due to a variety of factors, such as age, sex, and body mass index could affect the degrees of the relationship [239].

g. Indirect evidence suggests that PFAS metabolism is not linked to changes in lipid metabolism (which would suggest a reverse causation), thereby rejecting a hypothesis that both PFASs and cholesterol could be affected by a common cause that would produce apparent positive associations between PFASs and cholesterols in serum. Thus, subjects who are taking statins to decrease their serum-cholesterol do not show any lower serum-PFAS concentrations [60]. This report agrees with our findings in the Faroes (unpublished).

h. In the community survey in Bennington,[y] the Vermont Department of Health found a significant association between high cholesterol and the serum-PFOA concentration.

i. While early data from the 3M Cottage Grove production plant were reported to show no risk, an increased risk of cerebrovascular disease was indicated by a mortality study that relied on comparisons with the general population [240]. The subsequent

[x] Draft, dated October 11, 2001, PTX1799, vide supra.
[y] Vermont Department of Health. Exposure to Perfluorooctanoic Acid (PFOA) in Bennington and North Bennington, Vermont: Results of Blood Testing and Exposure Assessment, September 2017.

3M-supported follow-up [241] again showed strongly elevated risk of cerebrovascular death in workers with high exposure, especially when compared to an internal control group.

j. Cross-sectional NHANES data suggest that serum-PFOA concentration is associated with systolic blood pressure and the risk of hypertension [242]. Hypertension may relate to an increased risk of cerebrovascular mortality.

k. NHANES data suggest that increased serum concentrations of PFOA and PFOS are associated with an increased risk of chronic kidney disease, as defined by a low glomerular filtration rate [243].[z] The C8 Project examined association of serum PFOA levels with uric acid after adjustment for potential confounders. An increased risk of elevated uric acid was found in adults, including clinically defined hyperuricemia [244]. Again, this evidence is yet somewhat uncertain, as reverse causation may be present, i.e., due to the kidney disease preventing PFAS excretion via the urine [27]. Still, kidney toxicity could predispose to cardiovascular disease.

l. Epidemiological studies have rarely considered obesity as an outcome, but often included the body mass index (BMI) as a covariate [221], although adjustment for BMI may be inappropriate if obesity is an outcome of PFAS exposure. PFOA in stored pregnancy serum from a birth cohort of 422 subjects examined again at age 20 years was positively correlated (adverse effect) with body mass index (BMI) and other indicators of obesity [191].

m. Similar findings were reported from a birth cohort of 1,006 children in Boston [192], where higher prenatal exposure to PFOA, PFOS and PFHxS was associated with higher BMI, skinfold thicknesses and DXA assessment of total body fat, although only in girls at 7-8 years of age. Additional support derives from a birth cohort study that relied on joint data from Greenland and the Ukraine [193].

n. In Faroese children, born in 2007-2009, maternal pregnancy serum concentrations of PFOS and PFOA were associated with increased body mass index (BMI) and/or overweight risk at age 5 years [138].

o. Perhaps the most convincing evidence resulted from a randomized clinical trial, where obese subjects underwent calorie-restricted diets [245]. After multivariate adjustment, baseline PFAS concentrations were not significantly associated with concurrent bw or weight loss during the first 6 months. In contrast, higher baseline levels of PFASs were significantly associated with a greater weight regain, primarily in women. In women, comparing the highest to the lowest tertiles of PFOA concentrations, the multivariate-adjusted mean weight regain (SE) was 4.3 (0.9) versus 2.2 (0.8) kg (P_{trend} = 0.007) When further adjusted for changes in bw or thyroid hormones during the first 6 months, results remained similar.

[z] I note that the first author of this article, and co-author of five other publications on cardiovascular outcomes in PFOS-exposed populations, has provided erroneous information to the West Virginia University regarding his educational background. The articles in question were co-authored be established colleagues, and none of them has been retracted.

2. Toxicological evidence

a. Detailed discussion of elevated cholesterol and other risk factors in experimental models is included in recent evaluations by regulatory agencies [4, 56, 126]. The caveat expressed by 3M authors that rodents don't show elevated cholesterol at elevated PFAS exposures is no longer relevant due to the known species differences [5, 28].

3. Perspective

a. Due to the impact of covariates and the fact that cholesterol concentrations in the C8 study were lower than elsewhere in the U.S., selection bias in this study has been suggested [239]. However, although some selection forces likely played a role, there is little evidence to suggest that it caused bias away from the null hypothesis regarding PFOA exposure and cholesterol. EFSA considers this association likely to be causal [28].

b. The strongest associations in general refer to total cholesterol, but some studies have also examined lipoprotein fractions and found that especially low-density (LDL cholesterol) increases at higher serum-PFAS concentrations. Overall, the PFAS-associated increases in cholesterol are of sufficient magnitude to lead to a substantial impact on public health [246, 247].

c. Even if PFAS exposure explains only a small part of the variation in serum-cholesterol concentrations, still small increases in total and LDL cholesterol are associated with increased risks of cardiovascular disease. Some have noted that an increased mortality attributed to this cause has not been documented so far [9]. Thus, previous studies have suggested that cardiovascular mortality in PFAS workers is below expectation. However, this could arise from a healthy worker effect. Some evidence of increased risk 10 years after first employment was noted [37], as would be expected when the healthy-worker effects wears out.

d. Other serum parameters that may reflect kidney dysfunction, such as creatinine and blood urea nitrogen (BUN), were assessed in occupational studies. However, no clear associations with PFAS exposure biomarkers were reportedly found [235].

e. In regard to obesity, approximately one-third of adults and 17% of youth in the United States are obese [248]. Recent prospective studies of birth cohorts suggest that early-life exposures impact anthropometric measures in childhood and adolescence (see Section VIII.B.1). Given that obesity is already a serious public health problem, any increased risk due to PFOA exposure and the resulting impact on cardiovascular disease must be considered serious on its own.

f. For PFOA, EFSA considered the increase of serum cholesterol to be the critical effect associated with exposures in adults [28]. The benchmark dose level (BMDL) values from two studies corresponded to an estimated chronic intake of 0.8 ng/kg bw (body weight) per day, i.e., a TWI of 6 ng/kg bw per week. From this PTWI, a water limit of 3 ng/L can be calculated.

g. Screening for hypercholesterolemia is recommended for populations at risk, e.g., by the American Heart Association.[æ] Thus, lipid screening is an established procedure that is vital in detecting and managing lipid disorders that may be asymptomatic and may lead to cardiovascular disease [249]. Likewise, monitoring of bw and BMI is essential in preventing cardiovascular disease. Recommendations for identifying subjects for possible obesity interventions have been recently published [250].

F. Carcinogenicity

It is my opinion, based on the weight of the epidemiological evidence, and supporting toxicity evidence, that elevated PFOA exposures like those suffered by members of the Bennington Exposure Class result in an increased risk of harm to human health as carcinogens, and an increased risk of kidney and testicular disease, as already concluded by Dr. Ducatman.

Early studies in PFAS-exposed workers suggested a risk of prostate cancer, and support for this association comes from more recent studies that also include populations exposed at background levels. While early studies usually referred to cancer mortality, which is appropriate for sites like liver and pancreas due to the high fatality of these diseases, other sites are better explored using incidence data, while considering the impact of screening efforts, e.g., for prostate cancer.

A variety of subsequent studies demonstrate that PFAS exposure is associated with development of cancer at several sites. PFOA has been found to satisfy the EPA's criteria to be classified as "likely to be carcinogenic to humans" [251]. The IARC concluded last year that PFOA is a possible (Group 2B) human carcinogen [7]. The C8 Science Panel concluded that there is a probable link from PFOA exposure to testicular cancer and kidney cancer. All of these effects have been reported at background levels or at elevated exposures overlapping with those documented in Bennington residents. The main sites affected are the kidneys, testicles, prostate, and perhaps bladder and breast.

Based on the available evidence, exposure to PFASs has a substantial potential to cause cancer, most clearly for cancers of the kidneys and the testicles, and highly likely also for prostate cancer and bladder cancer. A possible risk of breast cancer is also of concern. The American Cancer Society (ACS) has issued several guidelines on early detection of these cancers for different age groups.[ø] These recommendations are of particular relevance to subjects with elevated exposures to PFOA.

[æ] http://www.heart.org/HEARTORG/Conditions/Cholesterol/Cholesterol_UCM_001089_SubHomePage.jsp.
[ø] https://www.cancer.org/healthy/find-cancer-early/cancer-screening-guidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer.html

1. Epidemiological evidence

Cancer risk assessments

a. In the most recent evaluation of cancer risk association with PFOA exposure, the IARC classified this substance as a possible human carcinogen (Group 2B) and concluded that there was relevant, though limited, evidence in humans that PFOA causes testicular and kidney cancer, while evidence for human carcinogenicity at other sites, such as bladder, prostate, thyroid, liver and pancreas was inadequate at the time of the evaluation; relevant evidence in experimental animals was also considered limited, in part due to the absence of a proper cancer bioassay [7].

b. The EPA's Science Advisory Board in 2006 reviewed the information available on PFOA at the time and suggested that the cancer data were consistent with the EPA Guidelines for Carcinogen Risk Assessment descriptor "likely to be carcinogenic to humans" [251].

c. As I describe in more detail below, the C8 Science Panel concluded that there is a probable link from PFOA to testicular cancer and kidney cancer. The C8 Panel conducted further studies, including an update of a previous occupational study [36]. Recent evidence suggests that additional cancer sites are affected by excess PFAS exposures and will be reviewed below.

Occupational studies

d. As described below, a dose-associated increased risk of kidney cancer was observed in workers in a fluoropolymer production plant in West Virginia, USA, and in the local community exposed to releases from the plant. Likewise, an increased risk of testicular cancer occurred in highly exposed local residents. Relevant evidence in humans also referred to other cancers [7].

e. Occupational mortality studies have been carried out in PFOS-exposed worker populations from a production plant in Alabama [240, 252] and PFOA-exposed workers from West Virginia [253] and Minnesota [254]. In evaluating this evidence, account must be taken of duration of exposure, exposure assessment methods, age at entry, and duration of follow-up, as discussed by IARC [7]. In addition, follow-up and case-control studies have focused on exposed communities. Some reports are not considered here, as small numbers of cases or other weaknesses make them less relevant to the evaluation. While the recent evaluation report relied on published evidence, some internal studies have been conducted in the past and provide some supplementary evidence. A key concern in these studies is the choice of comparison population, cf. the comments made above regarding the "healthy worker effect" (see section V.A.1).

f. In April 1989, DuPont issued an Internal Report, "An investigation into the occurrence of leukemia at Washington Works." The standardized mortality ratio was 2.1, but

was determined by DuPont not to be statistically significant.[å] Leukemia has not been considered in recent reports that mainly relied on mortality data, that are not a reliable source for hematopoietic cancer incidence.

g. In a subsequent report from 1992, DuPont examined the cancer surveillance data for 1956-1989 and mortality data for 1957-1991. For cancer, DuPont found a null result overall, but significant findings existed for specific sites, such as buccal cavity, pharynx, kidney and leukemia, among male employees (too few female employees). For mortality, mostly seen were deficit deaths (healthy worker effect) among males; among females, there was a significant excess of residual causes of deaths.[aa] Insufficient information is available to judge this report, but it illustrates that attention was paid to cancer risks early on.

Kidney cancer

h. Regarding kidney cancer, the C8 Panel concluded: "For kidney cancer, the worker mortality study conducted by the Science Panel showed a higher risk in the most highly exposed group compared to lower exposure groups among the workforce, but the risks were not elevated compared to the US population. In the cohort study, there was a gradient of increasing risk with increasing exposure but most strongly in the analyses that included exposure up to the time of diagnosis. When the 10 years of exposure prior to diagnosis was excluded, the association was less evident. No association was seen in the prospective analysis of cohort data, although the latter is limited by small numbers. In the geographic study, some results suggested an increasing risk of kidney cancer with increasing exposure and others did not. The science panel considers that the excesses observed indicate a probable link between PFOA and kidney cancer."

i. The C8 Panel reviewed and relied on several studies, as did the IARC working group. Increased risk of kidney cancer with a statistically significant exposure-response trend was reported in workers in a fluoropolymer production plant in West Virginia and in an exposed community near the plant [253, 255].

j. In further detail, elevated mortality from malignant kidney disease was documented among 5,791 workers exposed to PFOA in West Virginia [253]. No clear risk was seen in the small number of cases among PFOA-exposed workers from Minnesota [254]. However, community-based evidence [255, 256] showed an elevated incidence of kidney cancer associated with PFOA exposure.

Testicular cancer

k. The C8 report concludes: "For testicular cancer, there is evidence of a positive trend in risk across exposure groups, in some analyses, with the highest exposure group in both the internal analyses of the cohort study and the geographical cancer study showing

[å] AR226-1308-1.pdf, DuPont Internal Report, "An Investigation Into The Occurrence of Leukemia At Washington Works" (April 1989) (EID584220-30) DuPont Internal Final Report, "A Case-Control Study of Leukemia At the Washington Works Site" (12/3/91) (EID151953-65). Page EID584221.

[aa] AR226-1546. Washington Works Cancer Surveillance Data Mortality and Cancer Incidence. Pages EID521396 and EID521399.

estimated relative risks ranging from 3 to over 6 comparing the highest to lowest exposure groups. […] The high-exposure group, where the higher risk was observed, comprises only six cases therefore there remains some uncertainty. The Science Panel notes that there is experimental evidence of testis cancer being increased in exposed animals. The Science Panel considers observed excesses to indicate a probable link between PFOA and testicular cancer." The conclusions from IARC [7] are similar in regard to testicular cancer.

l. Mortality studies are unlikely to identify all cases of testicular cancer, and better evidence must rely on incidence data. The C8 Panel and IARC emphasized the results from the community study that documented an elevated incidence of testicular cancer at higher PFOA exposures in the Mid-Ohio River Valley near the production plant [255, 256].

Prostate cancer

Both prostate cancer and bladder cancer are diagnoses that may not necessarily appear on a death certificate, as the patient may die from some other disease, rather than the cancer, because the cancer may be curable or may not be fatal for several years. In addition, cancer risks in these types of studies are often calculated from small numbers of cases and may therefore not deviate with statistical significance from expectation. Thus, although the risk may not be significantly elevated, the upper confidence limit could be 5 or higher, suggesting that, at the same time, a 5-fold increased risk or greater cannot be ruled out. However, based on published evidence at the time, neither the C8 Panel nor the IARC considered prostate cancer a probable risk associated with PFOA exposure.

m. In a follow-up to 3M's 1989 mortality study carried out by Dr. Mandel, involving almost 3,000 male 3M workers at Cottage Grove from 1947 to 1983, ten years of employment in exposed jobs was associated with a statistically significant increase in prostate cancer mortality (more than three-fold). Still, this calculation was based on four cases among the exposed workers [35]. Unfortunately, comparisons with the general population of Minnesota probably biased the results of this study toward underestimated risks.

n. In 1993, Dr. Gilliland and Professor Mandel published a paper based on the new mortality study included in Gilliland's thesis.[bb] There were mostly null findings, except, as before, for prostate cancer (a 3.3-fold increase in mortality). Again, the number of cases was small (n = 6). The paper sought to explain the observed prostate cancer deaths as due to a purported higher prevalence of prostate cancer in Minnesota than the U.S. (control group) and/or as a chance finding.[cc] I note that Professor Mandel is a defense expert in this case.

o. In a mortality study of almost 4,000 employees exposed to PFOA, no clear tendencies were found for liver, pancreatic or testicular cancer. An increased standardized mortality ratio, however, was found for prostate cancer, and a 6.6-fold increased risk was found

[bb] AR226-0472.pdf, Frank S. Gilliland & Jack S. Mandel, Mortality Among Employees of a Perfluorooctanoic Acid Production plant, 35 JOM 950-954 (September 1993), with Summary of study. Page 003166.

[cc] AR226-0471. Jack S. Mandel & Leonard M. Schuman, "Mortality Study at the 3M Chemolite Plant" (January 1989), with Summary of study. Pages 003148-003149.

in workers with definite exposure. I note that the statistical significance relied upon two cases among the workers with known high exposure [241].

p. The most recent update is from a thesis completed in 2013.[dd] Using air monitoring results (and ignoring non-respiratory intakes and possible benefit from protective equipment), this study of 9,000 workers hired after 1947 compared deaths at the Cottage Grove production plant with those at the unexposed St. Paul plant through to 2002. When dividing the workers into six different exposure groups, a dose-dependent risk appeared for prostate cancer, although not statistically significant. The author of the thesis concluded that the results supported previous findings of a prostate cancer risk. However, in the published report [254] that was co-authored by 3M's Dr. Olsen, emphasis was on comparisons with the general population, no clear trend was found in quartile exposure groups, and the lack of association of prostate cancer with the exposure estimate was said to be in agreement with the findings in other studies. In discussing the possible risk factors, the Discussion section of the published article notes that family history of prostate cancer may play a role, although that was not taken into regard (see below under r).

q. In support of prostate cancer as a potential outcome of PFAS exposures, a nested case-control study of cancer incidence (based on diagnosis reporting, rather than mortality) in a Danish general population group focused on 713, 332, 128, and 67 cases of prostate, bladder, pancreatic, and liver cancers found during a follow-up of approximately 10 years after a baseline examination with blood sampling. At background exposures with a small variance, modest positive associations were found between serum concentrations of both PFOA and PFOS in regard only to prostate cancer morbidity [257].

r. A recent case-control study from Sweden showed similar serum-PFAS concentrations in 201 cases and 186 population-based controls. Heredity, i.e., a first-degree relative with the disease, was a risk factor, as has been documented before, and among those with a positive family history, elevated serum concentrations of both PFOA and PFOS were associated with a significantly increased risk of prostate cancer [258]. Accordingly, PFAS exposure may contribute to the etiology of this cancer type, although this may not be evident, unless family history is considered.

Bladder cancer

The current evidence is less strong as to bladder cancer, in part because mortality studies are unlikely to reflect this diagnosis, in part because incidence studies carried out relied on self-reports of past diagnoses. In addition, some studies included too few cases to support statistical analyses, and the two evaluations by the C8 Panel and IARC did not consider the evidence sufficient to draw a conclusion.

s. A study of PFOS-exposed workers showed that bladder cancer mortality was elevated among individuals with at least one year of exposure. I note that this finding was based on three deaths only, all of which occurred in workers deemed to have been highly exposed [240]. In addition, the results were obtained in comparison with the Alabama general

[dd] Cancer mortality in 3M chemical workers (PhD thesis by Katherine Koehler Raleigh). URL: https://conservancy.umn.edu/handle/11299/171701

population, and the low mortality ratio for lung cancer did not suggest that smoking was an important confounder.

t. In a subsequent reevaluation of the same cohort, mail questionnaires were used to include incident cases of bladder cancer. The incidence was not found to differ much from expectation, although an increased risk among the most highly exposed workers could not be ruled out [252]. The most recent follow-up by these authors used a job-exposure matrix to complement exposure estimates for comparison with cancer registry data; the findings do not support elevated bladder cancer risks otherwise observed in comparison with state averages, although the study cannot rule out the possibility of a risk [254]. Serum-PFAS measurements were available for many employees, but these data were considered. In addition, as smoking is a risk factor for bladder cancer, a comparison between rates for lung cancer and bladder cancer would have elucidated whether smoking-related cancer risks were similar in the occupational groups and in the comparison population. For example, the plausibility of a bladder cancer risk in fluoride-exposed workers [259] is supported by the observation of a greater increase in bladder cancer risk than in lung cancer risk among the workers, although the latter risk is much greater in smokers. The pattern was the same in the PFOA-exposed workers, with a greater excess in bladder cancer than in lung cancer.

Considering uncertainties in mortality data for bladder cancer, which is usually not fatal, and the wide confidence intervals associated with small numbers of cases, these studies showed non-significant associations, but could not rule out an effect of a magnitude that would be of substantial public health concern.

Other sites

u. Thyroid cancer seemed elevated in one analysis, and the same was true for pancreatic cancer [260]. Risk of liver cancer was apparently not elevated in any study [7]. In rodents, PFOA acts as a PPARα agonist, which is linked to the development of liver tumors, pancreas acinar cell adenomas, and Leydig cell tumors. Thus, in regard to tumor site, animal studies are not predictive of the most relevant sites in humans.

v. Apart from the focused studies referred to above, a recent review by the Institute of Medicine suggested that PFOA exposure may lead to breast cancer [261]. Likewise, the EPA's Science Advisory Board called attention to this potential, given the elevated occurrence of fibroadenomas and adenocarcinomas of the breast in two feeding studies in rats [262]. Although breast cancer may also be plausible from the evidence of endocrine disruption, only limited epidemiological support is at hand.

w. For example, a study of 31 breast cancer cases in Greenland found elevated current serum PFAS concentrations as compared to controls [263]. An extended study of 77 cases and 84 controls [264] again showed higher serum-PFAS concentrations in cases compared to controls, but similar differences also occurred in lipophilic contaminants (such as PCBs), and it is impossible at this time to determine the possible contribution by PFASs alone.

2. Toxicological evidence

a. Cancer effects in humans from PFASs are supported by experimental animal studies. The IARC evaluation considered the published evidence regarding mechanisms of PFOA-associated carcinogenesis to be moderate, which did not lead to a change in the overall classification of PFOA as a Group 2B carcinogen [7]. I understand that PFOA is currently being tested in a two-year bioassay by the National Toxicology Program.

b. PFOA was examined for carcinogenicity by the oral route of exposure in two studies in rats, with some initiation-promotion studies, as reviewed by the IARC in the evaluation discussed above [7].

c. The results from a rat bioassay sponsored by 3M were submitted to the EPA in 1983 and almost 30 years later released in a journal 2012 publication [265]. The results of this 2-year study documented dose-related PFOA-induced liver tumors and Leydig cell tumors of the testicles [266], and subsequent review suggested effects on pancreatic acinar cell adenoma and carcinoma, while mammary gland lesions were considered not to reflect possible breast cancer development [7].

d. Results from a second rat study showed elevated incidence of hepatocellular adenoma, testicular Leydig cell adenomas, and pancreatic acinar cell adenoma and carcinoma [267]. So far, no bioassay has been conducted in another mammal species.

e. In mice, PFOA exposure induced stromal hyperplasia in mammary glands at 18 months, an effect that is hypothesized to increase susceptibility for tumor growth in rodents and humans [10].

f. Certain scientists, particularly those at 3M, argue that a PPAR-related mechanism may explain liver carcinogenicity in some animal models. However, as discussed above, and as concluded in a recent risk assessment, both human and mouse PPAR-alpha are activated by PFOA *in vitro* [11]. EPA guidelines suggest that the non-PPAR dependent tumors, where available data do not justify establishing a rodent-specific mode of action, should be presumed to be relevant to humans [8, 117]. Still, the liver does not appear to be a primary target for cancer in humans.

3. Perspective

Evidence of carcinogenicity in humans can be equivocal, e.g., when occupational populations are small and relatively young, follow-up durations are short, historical exposure levels are uncertain, individuals have had simultaneous exposures to other compounds, when cancer cases may be incompletely ascertained, and when preexisting conditions may complicate the evaluation. The imprecise or incomplete data often limit the information that can be extracted from these studies [9]. Still, the weight of the evidence shows likely PFOA carcinogenicity, as the C8 Panel found for testicular cancer and kidney cancer [260].

When the numbers suggest a lack of statistical significance, that is only one side of the coin, as discussed in Section V.A. The other side regards the magnitude of a possible adverse effect that could have been overlooked, given the available data. Some researchers might

conclude that the absence of a statistically significant excess risk suggests that the risk is absent, while others, including myself, representing what is becoming the leading view, believe that such results must be interpreted in light of the total information at hand [43]. How large an effect could be overlooked or ignored as 'non-significant'? Often, available studies of young working populations with limited follow-up, possible incomplete ascertainment of cases, with healthy worker bias, and other limitations, cannot provide confidence that a risk is absent (see Table 1).

a. Regarding occupational mortality studies, a retrospective cohort study was completed in 1980 by Dr. Mandel in 1980 at the 3M Chemolite plant (Cottage Grove, Minnesota) site, as summarized in Dr. Gilliland's thesis [112]. No significant findings were observed, but the standardized mortality ratio for some cancers exceeded one (e.g., for cancer of the prostate and testis), a finding that should signal the need for further follow-up, given the anticipated healthy-worker effect and short follow-up time in the study.

b. In the mortality study of PFOA production workers carried out as part of Dr. Gilliland's thesis project, a 3.3-fold increase was seen in prostate cancer mortality compared to no employment in PFOA production, although based on only six prostate cancer deaths [35].

c. In a retrospective cohort mortality study from 1995 on 3M employees in Decatur, Alabama, data were collected through 1991. No significant excess in mortality was seen. Presumably, this may have been the origin of the observations on bladder cancer in workers employed through the end of 1997, published in 2003 [240]. A later follow-up report in 2007, also by 3M scientists, challenged those findings of excess bladder cancer, although the cancer outcome was now ascertained by postal questionnaire only [252].

d. At the request of the C8 Panel, a similar retrospective follow-up study in West Virginia included over 6,000 men and women employed during 1948-2002 and followed up through 2002. The results found little deviation that would suggest an excess cancer risk [36], although the findings as well could also not exclude the presence of an importantly elevated risk.

e. Among potential mechanisms for cancer development, immunotoxicity may be involved (see above Section A), and the IARC evaluation of PFOA [7] noted that genotoxicity was unlikely to explain the carcinogenic effects of PFOA.

f. Cancer is a serious disease where latent stages may be detected by periodic diagnostic medical examinations by established procedures, thereby allowing treatment at early stages where the outcome is more beneficial. The ACS has issued recommendations for cancer screening, and so has the Centers for Disease Control.[ee] For prostate cancer, measurement of the serum concentration of the prostate-specific antigen may be considered in conjunction with rectal exploration. Urinalysis is beneficial for early detection of kidney and bladder cancers, while regular scrotal examination is recommended for early detection of testicular cancer. These procedures are appropriate and necessary in the exposed populations and would differ from what would be a routine in the absence of exposure.

[ee] https://www.cdc.gov/cancer/dcpc/prevention/screening.htm

IX. RISK ASSESSMENT

Regulatory agencies vary somewhat in their approaches to risk assessment. Thus, ATSDR often considers human data too uncertain [4, 5], as they do not relate to intake levels, and ATSDR therefore relies primarily on animal toxicology results [5]. However, species differences occur, also for PFOA, particularly in regard to PPAR expression and excretion rates, thus complicating the translation of rodent data to the human situation. Regulatory agencies rely on animal toxicology, in part because they provide a clear association to intake levels, and comparisons based on serum concentrations then ensure comparison with epidemiological studies. In regard to genetic differences, the ATSDR has provided an extensive assessment that concludes that reliance of animal toxicology tests is appropriate {Agency for Toxic Substances and Disease Registry, 2018 #11931}. Of note, PPAR expression is only one of several key events that play a role in toxicity {Corton, 2018 #12057}.

A common concern in these evaluations is what an NRC committee [42] called the "untested chemical assumption," that a chemical is innocuous, unless toxicity testing has shown otherwise. Prominent scientists from the U.S. EPA commented recently that risk assessment has failed when adverse human health effects are demonstrated at exposure levels predicted from animal studies to be safe for humans [268]. That seems to be very true in regard to PFOA. Fortunately, other regulatory agencies have begun to consider epidemiological evidence, as illustrated by the recently released evaluation by EFSA [28]. Still, attention must be given to the caveats when drawing conclusions from incomplete evidence and the common biases toward the null hypothesis (Section V). For example, studies that fail to show statistical significance are often considered "null", even by ATSDR [5].

Regarding target organs, most regulatory risk assessments have focused on the liver, as rodent studies have clearly documented increased liver size and some functional changes as being strongly related to elevated PFAS exposures. In the recently released ToxProfile {Agency for Toxic Substances and Disease Registry, 2018 #11931}, ATSDR concludes that the liver, the immune system, and early development are most sensitive to adverse effects of PFOA exposure [5].

Still, the toxicology test studies have only in part covered the subtler effects that are of concern for human health, such as blood pressure elevations in pregnancy. Thus, reliance on animal studies may not protect adequately against adverse effects in humans.

Adverse effects on, e.g., immune functions and breast development have been recently documented at background PFAS exposure levels. Consequently, current limits for PFASs in drinking water recommended in the U.S. are insufficient to protect against adverse health risks, especially in vulnerable subgroups. Benchmark calculations based on decreased response to vaccine suggest that existing limits may be up to 100-fold too high [269], as I shall discuss below.

The UN Stockholm Convention in 2009 added PFOS and its precursors to the list of substances to be phased out (Annex B), and it seems that PFOA will likewise be included in the very near future. EChA has already listed PFOA and recently added PFHxS to the EU

Candidate List of substances of very high concern (SVHCs) for mandatory authorization procedures. These agencies clearly regard PFOA and associated PFASs a human health hazard.

A. Regulatory drinking water recommendations

The health advisories and water guidance levels identified by the EPA, individual states, and certain foreign governments and agencies vary from each other (see Table 4), based on values and assumptions used [241]. Differences between the acceptable limits are often due to differences in default values, e.g., for uncertainty factors used in the calculations, although estimates of water intakes and lifetime accumulation also differ. In addition, extended data show a clear tendency that limits decrease over time, as more evidence became available.

*Table 4. Applicable guidelines or exposure limits for PFOA (*sum of PFASs) in drinking water.*

Agency	Year	Value (ng/L)	Reference
Michigan	2013	11	http://www.michigan.gov/pfasresponse
Vermont	2016	20*	Vermont Agency of Natural Resources Department of Health Fact Sheet 11 April 2016
New Jersey	2017	14	https://www.nj.gov/dep/watersupply/pdf/pfoa-appendixa.pdf
Minnesota	2017	35	http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfoa.pdf
California	2018	14	https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/PFOA_PFOS.html
U.S. EPA	2016	70*	[269]

Most guideline values address individual PFASs, but some agencies have decided for a joint limit for PFOS and PFOA, and the Vermont limit was recently adjusted to refer to the sum of PFOA and four other PFASs. Recent toxicology evidence suggests that adverse effects from some PFASs may not be additive only, given that synergistic effects have been identified [270, 271]. However, the epidemiology offers little guidance, and toxicology studies suggest that at least PFOA has at least some mode of action that differs from PFOS [124, 272].

The present subsection will first summarize the most relevant regulatory guidances for concentrations in drinking water. The great variability in the numbers illustrated by the above table must be considered in light of changing needs for recommendations in different settings, emerging scientific insight, and the latency within regulatory agencies in regard to developing new guidelines. Also, the guidance has been developed based on different definitions and assumptions. In the subsequent subsection, I shall discuss the major approaches to setting exposure limits.

1. Federal and state drinking water recommendations

U.S. EPA

In 2009, the EPA issued provisional health advisories of 0.4 µg/L (400 ng/L) for PFOA, and 0.2 µg/L (200 ng/L) for PFOS [273]. At the time, EPA concluded that "[e]pidemiological studies of exposure to PFOA and adverse health outcomes in humans are inconclusive at present." Also, the evidence for the carcinogenicity of PFOS is considered "suggestive of carcinogenicity." Similar conclusions were drawn in 2015, when EPA updated their previously proposed guidelines for PFOA and PFOS in water to 0.07 µg/L (70 ng/L) for

both, as based on calculations relying on the most recent toxicological and supporting data [56, 126]. The U.S. EPA has selected 0.00002 mg/kg/day (or 0.02 µg/kg·d) as the Reference Dose (RfD) for PFOA and 0.00003 mg/kg/day (or 0.03 µg/kg·d) as the RfD for PFOS.

Agency for Toxic Substances and Disease Registry

The ATSDR first issued a draft toxicological profile in 2009, but concluded that there was insufficient evidence at the time to develop a minimal risk level [117]. The first updated version from 2015 [4] again focused on the experimental animal studies to develop a Minimal Risk Level (MRL) of 0.02 µg/kg·day for PFOA and 0.03 µg/kg·day for PFOS, as the only PFASs that had sufficient evidence to allow this calculation. The MRLs were the same as the EPA's RfDs.

The newly released and updated draft [5] relies heavily on research on PFOA exposure conducted by the C8 Science Panel. In addition, the report considers studies of people exposed to PFAS compounds at work and general population studies of people exposed to more prevalent background levels. PFASs have been "extensively evaluated in humans and laboratory animals," ATSDR concludes, but also that comparing toxicity across species is problematic, because the PFAS elimination half-lives are much longer in humans. The chemicals also cause different health problems in humans versus animals. The report also says: "In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive."

State limits and guidelines

While New Hampshire follows the U.S.EPA guidelines, Vermont established in 2016 its own legal limit for PFOA (and PFOS) in drinking water at 20 ng/L (Table 4). This limit has now been tightened to represent the sum of five PFASs, now also including PFHxS, PFHpA, and PFNA.[ff]

New Jersey's recently revised recommendations [11] took into account a human cancer risk assessment. Based on evidence on testicular cancer in rats, a cancer slope factor was calculated, and a lifetime risk of 1×10^{-6} was found to correspond to a water concentration of 14 µg/L. Almost the same level was found when using liver weight as a sensitive non-cancer outcome and taking into regard uncertainty factors. Previously, scientists from New Jersey used data on breast development in a rodent study to calculate BMDL for an endocrine disruption outcome [8]. In this case, the BMDL was translated to a tolerable serum-PFOA concentration in humans of 0.8 ng/mL, thus suggesting that endocrine disruption may occur at low exposure levels where immunotoxicity is otherwise the only adverse effect documented so far.

Several other states have decided on PFAS limits for drinking water. Limits published more recently tend to be lower. For example, the State of North Carolina used assumptions similar to those previously used by New Jersey. California recently published a guidance level of 14 ng/L. As far as I am informed, calculation of water limits was generally based on adverse outcome measures in animal studies (e.g., liver weight), and not driven by

[ff] Vermont Department of Health, http://www.healthvermont.gov/sites/default/files/documents/pdf/ENV_DW_PFAS_HealthAdvisory.pdf

epidemiological evidence. In addition, cancer and delayed breast development in animals have been considered as critical effects by the state of New Jersey only.

International limits and guidelines

The most recent evaluation from the EFSA [28] just released relied on both experimental and epidemiological data. The tolerable weekly intake limits for PFOA and PFOS are now 6 ng/kg bw and 13 ng/kg bw. The PFOA limit represents a decrease by more than 1000-fold, as compared with the previous limit from 2008. When transformed into water limits (assuming that water represents 20% of the PFAS intake), the limits are 3 ng/L and 6.5 ng/L. These limits are currently the lowest internationally and are based on a thorough and independent assessment that includes recent literature up to 2017.

B. Setting drinking water health limits

Generally speaking, a health limit is calculated from a "point of departure," which in turn is based on a calculation starting from a BMDL, or from a lowest-observed-adverse-effect level (LOAEL) or no-observed-adverse-effect level (NOAEL). The point of departure is usually derived from animal toxicity studies reflecting a point of critical effect. As cancer risk assessment has not been formally applied so far, the discussion here focuses on non-cancer risks.

The point of departure is then adjusted using knowledge of the half-life of the relevant PFAS in humans, and of the differences between humans and animals in the toxicity study in terms of water intake and retention, to arrive at a "human equivalent dose."

Then, because PFASs might not affect humans in exactly the same way that they affect, say, cynomolgus monkeys or laboratory rats tested in toxicity studies, the human equivalent dose is adjusted by applying "uncertainty factors" to arrive at an exposure limit. There are multiple types of uncertainty factors that may be appropriate, depending on the nature of the animal study, what is known about the differences between the animal in the study and humans, and the strength of the "database" of knowledge about the health effects of PFOA. One uncertainty factor that might be applied concerns potential differences in toxicodynamics. Another concerns intraspecies variability (recognizing that PFASs might affect human subpopulations differently, including more vulnerable populations such as children). The various uncertainty factors are then multiplied to arrive at a total uncertainty factor.

A relative source contribution (RSC) is often a default based on EPA guidance such as 0.2 (or 20%), representing an assumption that only 20% of a person's exposure to the PFAS comes from drinking water sources. Additional information about exposure sources is required for departing from the 0.2 default.

The various regulatory agencies appear to be in overall agreement in using a BMD model to calculate non-cancer health limits for drinking water [2]. In this method, a dose-response function is fitted to the data or adopted from a default assumption. The BMD is defined

as the dose which leads to a specific loss (or degree of abnormality) known as the benchmark response (BMR) in the outcome variable. The BMR must be specified before the analysis.

In epidemiological studies, a 5% change is often used for the BMR. A larger BMR will lead to a higher BMD. The statistical uncertainty in the BMD estimation is taken into account by calculating its lower one-sided 95% confidence limit, i.e., the BMDL. The BMDL is then used as the point of departure for calculation of the exposure limit.

Benchmark dose calculations for PFASs have been carried out using data from other toxicological studies, including a study in pregnant mice [274] and a study on breast development in pups [8]. The New Jersey committee [11] showed that these findings would result in an RfD as low as 0.11 ng/kg·d. When modeling the results in terms of serum-PFOA concentrations, they showed that the Target Human Serum Level (analogous to the RfD expressed on a serum level basis) would be 0.8 ng/mL, i.e., below the median serum PFOA level in the U.S. general population. Again, the New Jersey committee refrained from using this information for calculating a drinking water limit.

Recent evidence have identified adverse effects of PFASs on sensitive outcomes in laboratory animals following developmental exposure [10] and on immune system functions in children [91]. It is then appropriate to consider likely effects that target the programming of organ system function and future disease risks [275]. When developmental toxicity is likely, a National Research Council committee 20 years ago proposed to include an extra 10-fold uncertainty factor to protect children against food contaminants [69]. Such factor has apparently not been used for water-PFAS exposures so far, although immunotoxicity may be a hazard that primarily affects early development.

C. Recent guidelines and benchmark dose calculations

In our recent study of immunotoxicity [91], PFASs were measured in serum to assess prenatal and postnatal exposure in regard to associations with concentrations of two specific antibodies against childhood vaccines. The antibody responses could be categorized either in terms of the concentration as such or whether it was below the clinically protective concentration of 0.1 IU/mL. We calculated that the BMDL for the serum-PFOA concentrations at age 5 years are 0.6 and 1.0 ng/mL serum for tetanus and diphtheria antibody concentrations at age 7 [269]. These results are much below the BMDL values from animal studies, and they are also in the low range of current background exposures. These results indicate that adverse effects occur below current regulatory guidelines.

Table 5. Summary of guideline values (ng/L) for PFOS and PFOA in drinking water, as compared with the estimated limit corresponding to the BMD calculations [269].

Authority	Year	PFOS	PFOA
U.S. EPA	2016	70	70
ATSDR*	2018	7	11
EFSA*	2018	6.5	3
BMDL-based	2013	<1	<1

*Estimated from tolerable weekly intake levels, assuming 20% exposure contribution from water consumption.

Some uncertainties remain and probably result in underestimations of the risk, and the results may therefore be biased toward higher and less protective levels. We applied standard default factors that correspond to routine practice within the EPA and other regulatory agencies. Our calculated water-PFOA limit based on immune-system effects suggests that current exposure limits in the United States remain too high. Thus, even when compared to the most recent guidelines or limits for PFOS and PFOA in drinking water, the recently lowered levels still appear too high to be protective (Table 5).

X. INCREASED RISK IN THE EXPOSED POPULATION AND RECOMMENDATIONS FOR PERIODIC DIAGNOSTIC TESTING

As discussed in section V.A, there are important tendencies that will result in underestimations of PFAS toxicity. Also, reliance on animal toxicity data with a focus on enlarged livers and similar routine outcomes from rodent toxicity studies can greatly underestimate the risk to human health [268]. More targeted studies on immunotoxicity and endocrine disruption in mice revealed adverse effects at much lower exposures than those that lead to liver damage, most clearly when exposures were determined from blood concentrations and not on the amount in the feed. Subsequently, human studies demonstrated that deficient antibody responses to routine vaccinations occur at elevated background PFAS exposures. Supporting studies showing more frequent infectious disease in children at higher PFAS exposure emphasize that the immune system is a highly vulnerable target organ. Thus, recent scientific insight suggests that, as it relates to children's immune systems and endocrine disruption, further consideration of protective levels may be necessary.

As an indication how new data can reveal adverse effects at exposure levels previously thought to be safe, the ATSDR Toxicology Profile in 2009 concluded that no data were available on immunotoxicity in humans [117], but the authors did not know that our study in the Faroes was under way and was to be published in 2012 [91]. Subsequent versions of the ATSDR review have increasingly considered epidemiological evidence and most recently tightened the recommended MRLs by about a 10-fold factor [5]. The recent report from the NTP considers PFOS and PFOA "presumed" immunotoxicants, which is the level just below "known" [6]. This conclusion has not yet impacted risk assessments carried out by regulatory agencies at state level or otherwise. However, EFSA refers to immunotoxicity as a critical effect in humans in its opinion just released [28].

Given the fact that much of the leading scientific literature is fairly recent (see Figure 1), the conclusions that can be drawn at this point must be regarded preliminary and likely conservative to some extent, as they may represent underestimations of the health risks. Our current understanding is very different from 2008 when the first formal risk assessments were published [1, 276]. At the present time, the main uncertainty regards effects on the most vulnerable target organs and critical exposure conditions, such as prenatal exposures, that have yet to be studied in sufficient depth. The most appropriate conclusion that can be drawn is that adverse effects on breast development, on adaptive immune system development and elevations of serum-cholesterol concentrations likely represent critical effects and that BMDLs should

focus on these outcomes. Although EFSA attempted to do that [28], the availability of data in deciles or other groupings resulted in substantial overestimations of the BMDLs. In this light, my above conclusions may well be underestimated.

A. Recommendation for periodic diagnostic testing

PFOA is a known health hazard in humans, and exposures must be limited to the extent possible. As this hazardous chemical remains in the body for many years, medical monitoring is recommended in exposed populations to identify latent stages of serious diseases by established screening methods that are useful in detecting early and treatable disease states.

Medical monitoring is reasonably necessary to identify subclinical or latent forms of PFOA-associated disease pathogeneses, as this will help protecting the defined Exposure Class against the increased risk of disease as a consequence of their elevated PFOA exposures. In agreement with the preliminary criteria for medical monitoring issued by the Court,[gg] the monitoring should differ from that provided to anyone who sees a doctor regularly and be useful for the early identification of injury associated with the exposure. In my opinion, Dr. Ducatman's proposal for medical monitoring of the Class of exposed Bennington residents is well justified.

As discussed in Section VIII, PFOA-associated adverse effects relate to several organ systems. For all of these organ systems, a variety of monitoring options are available and known to be efficient in allowing intervention at an early stage. In his reports, Dr. Ducatman has spelled his proposed clinical monitoring to cover the major outcomes.

Every individual has his or her own background risk of developing the diseases in question, but all current and former Bennington residents who will comprise the Exposure Class will be adversely affected by their PFOA exposure from ingestion of PFOA-contaminated drinking water. Early-life exposures will likely lead to greater risks, as will exposures occurring during pregnancy or at peak ages for, say, cancer development. Still, monitoring blood pressure during pregnancy would not be needed for male residents, and screening for prostate cancer not needed for females. Age should also be considered. Other factors would be hard or impossible to decipher beforehand to allow a targeted monitoring program. However, such factors should appropriately be considered when determining the frequency of the monitoring of the exposed individuals.

The defense experts agree on the overall criteria for medical monitoring, but they add additional demands, e.g., for proof of efficacy, appropriateness of costs, minimizing adverse effects (see Calabrese at 29, Guzelian at 10 and Mandel at 7). While these considerations are reasonable in a public health connection, they are not appropriate in a case like this, where Bennington residents have been exposed to a documented health hazard without their knowledge or consent, and where the accumulated burden of the toxicant is associated with long-term adverse health consequences, many of which can be detected at an early, latent stage, where medical intervention will likely be beneficial. The demands of the defense experts would require additional studies of the Bennington residents and those at other locations for many years to

[gg] [Doc. 105, at 6].

generate the documentation demanded, i.e., essentially observing the occurrence of exposure-related disease without proper intervention. I can see no justification for these demands.

Given the diverse characteristics of the exposed population and the overall evidence on water-mediated exposures and the associated adverse health effects, it is also not possible to generate calculations of anticipated benefits apart from concluding that they, in my judgment, will be substantial.

XI. SUMMARY OF REBUTTAL OPINIONS

1) Two of the defense experts, Drs Calabrese and Guzelian, have not contributed to research on PFAS exposure and toxicity, and the third expert, Dr, Mandel, has written industry-sponsored publications that have attempted to minimize or disguise exposure-related adverse health effects in PFOA-exposed company employees. Their opinions cannot be accepted as a neutral assessment of the risks associated with the PFOA exposures in the Bennington Zone of Contamination.

2) The defense experts rely on strict criteria for causality rather than an assessment of the weight of the evidence, as applied by agencies, such as ATSDR, EPA, NTP, EFSA, and IARC. The defense experts' conclusions that no adverse health effects are likely are the result of such unnecessarily strict criteria and a subsequent dismissal of solid and prospective epidemiological evidence that has been relied upon by regulatory agencies and is generally accepted within the medical community.

3) One of the defense experts, Professor Guzelian, repeatedly refers to his own definition of 'evidence-based toxicology' as the appropriate basis for decision-making. However, these strict criteria are inappropriate for real-world risk assessment and have not been applied by regulatory agencies or the scientific/medical community at large.

4) The defense experts criticize Dr. Ducatman for cherry-picking from the literature and reaching biased conclusions, when in fact the defense experts are doing that themselves.

5) The defense experts assume that there is no risk (or no increased risk) unless there is convincing evidence to the contrary. Rather than assessing the overall evidence, its plausibility given available toxicological support, and the statistical power of the epidemiological evidence, the defense experts disregard all cross-sectional studies and also ignore strong prospective evidence to allow a conclusion that no exposure-related risk is present. Such an approach is not justified.

6) Based on the weight of the epidemiological evidence and supporting toxicity evidence, I find that elevated exposure to PFOA, like those suffered by members of the Bennington Exposure Class. results in an increased risk of harm to at least human immune system functions; reproductive functions including adverse effects to the next generation; endocrine functions, including increased risk to thyroid disease and diabetes; liver function; and by increasing the risk of cardiovascular disease and certain types of cancers.

7) The defense experts also reject the occurrence of highly elevated serum-PFOA concentrations as evidence of increased exposure from the contaminated drinking water, thus also rejecting any presence of risk from the exposures. However, no justification is provided other than disregarding the studies that have convincingly shown that PFOA-associated health risks exist within background ranges of exposures.

8) The defense experts agree that appropriate monitoring methods exist, but they insist that additional criteria be fulfilled, such as efficacy and overall benefits. Although evidence on these aspects would be desirable, it is unrealistic to obtain such detailed information in the present case. If estimates of efficacy and benefits were required to be provided, there would be no meaningful way to justify medical monitoring without actually instituting the monitoring and obtaining detailed information on its success.

9) I find that Dr. Ducatman's conclusions on increased risk and need for medical monitoring are justifiable and reasonable on the basis of current scientific and medical evidence, and the PFOA analyses from the Bennington Zone of Contamination, as judged from my own background as a physician and epidemiologist and my long-term research on adverse effects of PFASs in exposed populations.

XII. AFFIRMATION

I affirm under penalty of perjury that the foregoing is a true and correct statement of my opinions in this matter and the grounds for those opinions.

Philippe Grandjean
1 August , 2018

EXHIBIT A

ABBREVIATIONS

ACS	American Cancer Society
ALT	alanine transaminase
ANA	antinuclear antibody
APFO	ammonium perfluorooctanoate
AP	alkaline phosphatase, liver enzyme
AST	aspartate aminotransferase, liver enzyme
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose level
BMR	benchmark response
BUN	blood urea nitrogen
bw	body weight
C-8	perfluorinated octanol compounds
CAR	constitutive androstane receptor
CDC	Centers for Disease Control and Prevention
CI	confidence interval
ECHA	European Chemicals Agency
EEA	European Environment Agency
EFSA	European Food Safety Authority
ER	estrogen receptor
EPA	Environmental Protection Agency
FEP	fluorinated ethylene propylene
FSH	follicle-stimulating hormone
GGT	gamma-glutamyl-transferase, liver enzyme
HDL	high-density lipoprotein
IARC	International Agency for Research on Cancer
LDL	low-density lipoprotein
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
NAFLD	non-alcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect level
NRC	National Research Council
NTP	National Toxicology Program
OR	odds ratio
PCB	polychlorinated biphenyls
PFAS	perfluorinated alkylate substance
PFHxS	perfluorohexane sulfonic acid
PFHpA	perfluoroheptanoic acid
PFNA	perfluorononanoic acid

PFOA	perfluorooctanoic acid;
PFOS	perfluorooctane sulfonic acid
PPAR	peroxisome proliferator activated receptor
PXR	pregnane X receptor
RfD	reference dose
RsC	relative source contribution
T2D	type 2 diabetes
T3	triiodothyronine
T4	thyroxine
TOF	total organic fluorine
TSH	thyroid-stimulating hormone
WHO	World Health Organization

EXHIBIT B

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Academic degrees
1974, M.D., University of Copenhagen
1975, Diploma in basic medical research, University of Copenhagen
1979, D.M.Sc. (dr.med.), University of Copenhagen

Chronology of employment

1974-1975	Postgraduate training fellowship, University of Copenhagen
1975-1978	Research fellow, Institute of Hygiene, Univ. Copenhagen
1978-1980	Senior research fellow, University of Copenhagen
	Visiting fellow, Department of Community Medicine,
	Mount Sinai School of Medicine, New York
1980-1982	Director, Department of Occupational Medicine,
	Danish National Institute of Occupational Health
1982-	Professor of Environmental Medicine, Odense University
1983-2017	Consultant in Toxicology, Danish Health Authority
1994-2002	Adjunct Professor of Public Health (Environmental Health)
	and Neurology, Boston University School of Medicine
2003-	Adjunct Professor of Environmental Health, Harvard School of Public Health

Awards and honors

Prize essay in medicine, University of Copenhagen (1972)
Fulbright senior research scholarship (1978)
Keynote speaker, Odense University anniversary (1983)
Gitlitz Memorial Lecture, Association of Clinical Scientists, USA (1985)
Knight of the Dannebrog, awarded by the Queen of Denmark (1990)
The Dannin prize for medical research (1991)
Fellow, American Association for the Advancement of Science (1994)
Irish Congress Lecturer, Royal College of Physicians of Ireland (1996)
Knight of the Dannebrog, First Degree, awarded by the Queen of Denmark (2003)
'Mercury madness award' for excellence in science in the public interest from eight US environmental organizations (2004)
Emeritus Fellow, International Union of Pure and Applied Chemistry, IUPAC (2009)
Honorary Research Award, International Order of Odd Fellows (2010)
Science Communication Award, University of Southern Denmark (2012)
Bernardino Ramazzini Award (2015)
Basic & Clinical Pharmacology & Toxicology Nordic Award (2015)
Margrethegaarden honorary prize (2016)
John R. Goldsmith Award, International Society for Environmental Epidemiology (2016)

Editorial boards
American Journal of Industrial Medicine (1987-2017)
Applied Organometal Chemistry (1985-1991)
Arbejdsmiljø (Occupational Environment, in Danish, 1983-1990)
Archives of Environmental Health (European Editor, 1986-1992)
Archives of Toxicology (1987-)
Biomarkers (1996-2001)
Central European Journal of Occupational and Environmental Medicine (2015-)
Critical Reviews in Toxicology (1985-2012)
Danish Medical Bulletin (1994-2003)
Environmental Health (Editor-in-Chief, 2002-)
Environmental Health Perspectives (2003-)
Environmental Research (1981-1994 and 2014-, Associate Editor, 1995-2014)
Industrial Health (2000-2005)
International Journal of Hygiene and Environmental Health (2001-)
International Journal of Occupational and Environmental Health (1994-2011)
International Journal of Occupational Medicine & Environ Health (1991-
Journal of Clean Technology, Environmental Toxicology, and Occupational Medicine (1992-1998)
Journal of Environmental Medicine (1998-1999)
Naturens Verden (Natural Science, in Danish) (1987-1991)
Ugeskrift for Læger (Danish Medical Journal, in Danish) (1991-2007)

Scientific societies
American Association for the Advancement of Science (Fellow, 1994)
American Public Health Association
Collegium Ramazzini (Fellow, 1987; Member of the Council, 2005-2013)

Danish Medical Association
Danish Societies of Clinical Chemistry, Epidemiology, Occupational and Environmental Medicine, and Public Health
Faroese Society of Science and Letters
International Commission on Occupational Health
International Society for Environmental Epidemiology

Research support as Principal Investigator since 2000
2000-2006 NIEHS
Mercury associated neurobehavioral deficit in children
2001-2003 Nordic Arctic Research Programme (NARP)
Changing patterns of biomagnified pollutants in the northern marine environment
2001-2004 Danish Medical Research Council
Exposure assessment for endocrine disruptors
2002-2004 Danish Medical Research Council
Environmental epidemiology research
2003-2004 European Commission
Assessment of Neurobehavioral Endpoints and Markers of Neurotoxicant Exposures (ANEMONE)
2003-2005 Danish Medical Research Council
Research in hormone related substances
2003-2006 NIEHS ES11687
Effects of perinatal disruptors in children
2003-2007 EPA STAR RD-83075801-0
Children's vulnerability to environmental immunotoxicant
2004-2011 NIEHS ES12199
Epidemiology of immunotoxicant exposure in children
2006-2011 NIEHS ES13692
Health effects of lifetime exposure to food contaminants
2006-2012 NIEHS ES14460
Three-generation human study of reproductive effects of marine food contaminants
2008-2012 Danish Council for Strategic Research
Environmental pollutant impact on antibody production against current and new childhood vaccines
2007-2013 NIEHS ES009797
Mercury associated neurobehavioral deficit in children

Major Current Funding as Principal Investigator
2011-2017 NIEHS ES012199
Epidemiology of immunotoxicant exposure in children
2012-2018 NIEHS ES021993 and NSF OCE-1321612
Immunotoxicity in Humans with Lifetime Exposure to Ocean Pollutants
2013-2018 NIEHS ES021477
Glucose Metabolism in Adults Prenatally Exposed to Diabetogenic Pollutants
2013-2018 NIEHS ES021372
Pollutant-related diabetes in the Nurses' Health Study II

2014-2017 NIEHS ES023376
Gut Microbiome in Adults with Early Life Exposures to Environmental Chemicals
2017-2022 NIEHS P42ES027706
Sources, Transport, Exposure and Effects of PFASs (STEEP)

Major committees, boards and elective offices

Danish:

Danish Medical Association: Member, Prevention Council (2011-2014)
Danish Medical Research Council: Consultant on environmental medicine (1985-1990); Member, Joint Research Council Committee on Environmental Research (1986-1991); Member of DMRC (1992-1998)
Danish Society of Community Medicine: Secretary (1977-1978)
Danish Society of Industrial Medicine: Board Member (1974-1983)
Ministry of Education: Member, Committee on Toxicology (1984-1986); Member, Committee on Environmental Education (1986-1987)
Ministry of the Environment: Member, Council on Environmental Chemicals (1983-1989); Member, Environmental Appeal Board (1986-2010); Member, Environmental Research Council (1990-1992); Member, Advisory Committee on Pesticide Research (1995-2004); Member, Advisory Committee on Arctic Research (1996-2004)
Ministry of Health: numerous committee appointments; Chair, Committee on Risk Perception (2000-2001)
Ministry of Labour: Consultant on Occupational Health, Council on Occupational Safety and Health (1983-1993); Member, Occupational Health Council Research Committee (on behalf of the Danish Medical Research Council) (1984-1990 and 1999-2003)
Ministry of Research: Chair, Committee on Research at the Faroe Islands (1995-1996); Member, Committee on Scientific Dishonesty (2004-2006); Chair, Committee on Non-Ionizing Radiation (2004-2009)
Odense University (from 2000 University of Southern Denmark), elected offices: Chairman, Institute of Community Health (1982-1985; 1996-1999); Member of Executive Committee, Institute of Community Health (from 2000 Institute of Public Health) (1986-1995; 2000-2005); Member, Faculty Research Committee (1983-1985); Member, Curriculum Committee (1984-1986); Member, Faculty Council (1985-1993); Vice-Dean (1991-1993); Member, Scientific Integrity Committee (2003-)

United States and international:

Academy of Finland: member of panel evaluating the National Institute of Public Health (1995), site visit of center of excellence (2001)
Agency for Toxic Substances and Disease Registry: Workshop Rapporteur, Neurobehavioral Test Batteries for Use in Environmental Health Field Studies (1992); Member, Expert Panel of Mercury (1998)
Association of Schools of Public Health in the European Region: Treasurer (1975-1977)
BioMedCentral: Member, Editors Advisory Group (2011-2013)
Boston Environmental Hazards Center: Consultant (1994-1999)
Collegium Ramazzini: President, International Conference, The precautionary principle: Implications for research and prevention in environmental and occupational health (2002); Member, Executive Council (2005-2013)

Commission of the European Communities: National Expert, Working Party on Environmental and Lifestyle-Related Diseases (1988-1990); ad hoc Consultant for evaluation of research applications; ad hoc Scientific Advisor on Risk Assessment (2009-); Member, SCHER Working group on Dental Amalgam (Human Health) (2012-2013)
European Environment Agency: Member, Scientific Committee (2012-2018)
European Food Safety Authority: Member, Panel on Contaminants in the Food Chain responsible for 85 opinions (2003-2009); Member of Working Groups on mercury, polychlorinated biphenyls, cadmium, lead, and benchmark dose
Food Advisory Committee, U.S.FDA, Methylmercury: invited expert (2002)
INMA (Infancia y Medio Ambiente), Spain: Member, Project Steering Committee (2010-)
Institut de Recherche Santé, Environnement et Travail, France: Member, Board of Advisers (2015-)
International Agency for Research on Cancer: Member of Task Group, Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 47 (1988), Vol. 49 (1989), as chairman, Vol. 58 (1993), and as Subgroup chair, Vol. 100C (2009)
International Commission on Occupational Health: Danish Delegation Secretary (1982-90); Member, Scientific Committee on the Toxicology of Metals (1987-); Member of the Board (1990-1996)
International Programme on Chemical Safety: Member of Task Group, Environmental Health Criteria, Vol. 36 (1984) and 72 (1986)
International Society for Environmental Epidemiology: Councillor (1991-1994)
International Union of Pure and Applied Chemistry: Member, Subcommittee on the Toxicology of Nickel (1979-1989); Titular Member (1985-1991) and Chairman (1987-1991), Commission on Toxicology; Chairman, Subcommittee on Risk Assessment (1985-1989)
Karolinska Institute (Stockholm, Sweden): Member of international evaluation panel on environmental medicine (1993)
Ministry for Scientific Policy (Belgium): Consultant on national research program on health hazards (1990 and 1994)
National Institutes of Health (USA): Member of Special emphasis panels (2009-)
NATO Priority Area Panel on Environmental Security: Member (1996-1997)
Norwegian Research Council: ad hoc reviewer (2001-2008); Chairman of Environment and Health Review Group (2009-2010); member of steering committee (2011-2015)
Prenatal programming and Toxicity (PPTOX) conferences: Organizer/Chair/ Co-chair, Torshavn (2007), Miami (2009), Paris (2012), Boston (2014), Kita-Kyushu (2016)
Society of Occupational and Environmental Health: Member, Governing Council (1990-1993)
Swedish Council for Work Life Research: Member, Priority Committee on Chemical Health Risks (1997-1998)
U.N. Environment Programme: Member, Global Mercury Assessment Working Group (2002)
U.S. Environmental Protection Agency: Member, SAB/SAP Endocrine Disruptor Screening Program Subcommittee (1998-1999); Member, Food Quality Protection Act (FQPA) Science Review Board (SRB)(1999-2003)
White House Office of Science and Technology Policy: Team leader and presenter, Workshop on Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury (1998)
World Health Organization: Temporary Adviser or Consultant on several occasions, five times elected Rapporteur; Member, European Advisory Committee on Health Research (2011-)

EXHIBIT C

LIST OF GRANDJEAN PUBLICATIONS FROM RECENT 10 YEARS

Publications in international peer-reviewed journals

167. Grandjean P, Budtz-Jørgensen E. Total imprecision of exposure biomarkers: Implications for calculating exposure limits. Am J Industr Med 2007; 50: 712-9.
168. Grandjean P. Methylmercury toxicity and functional programming. Reproduct Toxicol 2007; 23: 414-20.
169. Grandjean P, Murata K. Developmental arsenic neurotoxicity in retrospect (editorial). Epidemiology 2007; 18: 25-6.
170. Wermuth L, Bech S, Petersen MS, Joensen P, Weihe P, Grandjean P. High prevalence and incidence of Parkinson's disease in the Faroe Islands. Acta Neurol Scand 2008; 118: 126-31.
171. Murata K, Grandjean P, Dakeishi M. Neurophysiological evidence of methylmercury neurotoxicity. Am J Industr Med 2007; 50: 765-71.
172. Budtz-Jørgensen E, Grandjean P, Weihe P. Separation of risks and benefits of seafood intake. Environ Health Perspect 2007; 115: 323-7.
173. Andersen HR, Nielsen F, Nielsen JB, Kjaerstad MB, Baelum J, Grandjean P. Xeno-oestrogenic activity in serum as marker of occupational pesticide exposure. Occup Environ Med 2007; 64: 708-714.
174. Andersen HR, Schmidt IM, Grandjean P, Jensen TK, Budtz-Jørgensen E, Kjaerstad MB, Baelum J, Nielsen JB, Skakkebaek NE, Main KM. Impaired reproductive development in sons of women occupationally exposed to pesticides during pregnancy. Environ Health Perspect 2008; 116: 566-72.
175. Petersen MS, Halling J, Damkier P, Nielsen F, Grandjean P, Weihe P, Brøsen K. Polychlorinated biphenyl (PCB) induction of the CYP3A4 enzyme activity in Healthy Faroese adults. Toxicol Appl Pharmacol 2007; 224: 202-6.176. Choi AL, Budtz-Jørgensen E, Jørgensen PJ, Steuerwald U, Debes F, Weihe P, Grandjean P. Selenium as a potential protective factor against mercury developmental neurotoxicity. Environ Res 2008; 107: 45-52.
177. Grandjean P. Seven deadly sins of environmental epidemiology and the virtues of precaution. Epidemiology 2008; 19: 158-62.
178. Grandjean P. Late insights into early origins of disease. Basic Clin Pharmacol Toxicol 2008; 102: 94-9.
179. Petersen MS, Weihe P, Choi A, Grandjean P. Increased prenatal exposure to methylmercury does not affect the risk of Parkinson's disease. Neurotoxicology 2008; 29: 591–5.
180. Petersen MS, Halling J, Bech S, Wermuth L, Weihe P, Nielsen F Jørgensen PJ, Budtz-Jørgensen E, Grandjean P. Impact of dietary exposure to food contaminants on the risk of Parkinson's disease. Neurotoxicology 2008; 29: 584–90.
181. Halling J, Petersen MS, Brosen K, Weihe P, Grandjean P. Genetic predisposition to Parkinson's disease: CYP2D6 and HFE in the Faroe Islands. Pharmacogenet Genomics 2008; 18: 209-12.
182. Choi A, Cordier S, Weihe P, Grandjean P. Negative confounding in the evaluation of toxicity: The case of methylmercury in fish and seafood. Crit Rev Toxicol 2008; 38: 877-93.
183. Grandjean P, Ozonoff D. Environmental Health: the first five years. Environ Health 2007; 6: 27.

184. Grandjean P, Choi A. The delayed appearance of a mercurial warning. Epidemiology 2008; 19: 10-1.
185. Pouzaud F, Ibbou A, Blanchemanche S, Grandjean P, Krempf M, Philippe H-J, Verger P. Use of advanced cluster analysis to characterize seafood consumption patterns and methylmercury exposures among pregnant women. J Exp Anal Environ Epidemiol 2010; 20: 54-68.
186. Grandjean P, Perez M. Developmental neurotoxicity: Implications of methylmercury research. International Journal of Environment and Health 2008; 2: 417-28.
187. Choi AL, Grandjean P. Methylmercury exposure and health effects in humans. Environ Chem 2008; 5: 112-20.
188. Weihe P, Kato K, Calafat AM, Nielsen F, Wanigatunga AA, Needham LL, Grandjean P. Serum concentrations of polyfluoroalkyl compounds in Faroese whale meat consumers. Environ Sci Technol 2008; 42: 6291-5.
189. Grandjean P, Budtz-Jørgensen E, Barr DB, Needham LL, Weihe P, Heinzow B. Elimination half-lives of polychlorinated biphenyl congeners in children. Environ Sci Technol 2008; 42: 6991–6.
190. Coccini T, Manzo L, Debes F, Weihe P, Grandjean P. Application of lymphocyte muscarinic receptors and platelet monoamine oxidase-B as biomarkers of CNS function in a Faroese children cohort prenatally exposed to methylmercury and PCBs. Biomarkers 2009; 14: 67-76.
191. Budtz-Jørgensen E, Debes F, Weihe P, Grandjean P. Structural equation models for meta-analysis in environmental risk assessment. Environmetrics 2010; 21: 510-27.
192. Choi AL, Weihe P, Budtz-Jørgensen E, Jørgensen PJ, Salonen JT, Tuomainen T-P, Murata K, Nielsen HP, Petersen MS, Askham J, Grandjean P. Methylmercury exposure and adverse cardiovascular effects in Faroese whalingmen. Environ Health Perspect 2009; 117: 369-72.
193. Bjørling-Poulsen M, Andersen HR, Grandjean P. Potential developmental neurotoxicity of pesticides used in Europe. Environ Health 2008; 7: 50.
194. Julvez J, Grandjean P. Neurodevelopmental toxicity risks due to occupational exposure to industrial chemicals during pregnancy. Industr Health 2009; 47: 459-68.
195. Grandjean P, Budtz-Jørgensen E. An ignored risk factor in toxicology: The total imprecision of exposure assessment. Pure Appl Chem 2010; 82: 383-91.
196. Kirkegaard M, Sonne C, Dietz R, Letcher RJ, Jensen AL, Hansen SS, Jenssen BM, Grandjean P. Alterations in thyroid hormone status in Greenland sledge dogs exposed to whale blubber contaminated with organohalogen compounds. Environ Qual Saf 2011; 74: 157-63.
197. Blair A, Saracci R, Vineis P, Cocco P, Forastiere F, Grandjean P, Kogevinas M, Kriebel D, McMichael A, Pearce N, Porta M, Samet J, Sandler DP, Costantini RS, Vainio H. Epidemiology, public health and the rhetoric of false positives. Environ Health Perspect 2009; 117: 1809-13.
198. Schlezinger JJ, Bernard PL, Haas A, Grandjean P, Weihe P, Sherr DH. Direct assessment of cumulative aryl hydrocarbon receptor agonist activity in sera from experimentally exposed mice and environmentally exposed humans. Environ Health Perspect 2010; 118: 693-8.
199. White RF, Palumbo CL, Yugelun-Todd DA, Heaton KJ, Weihe P, Debes F, Grandjean P. Functional MRI approach to developmental methylmercury and polychlorinated biphenyl neurotoxicity. Neurotoxicology 2011; 32: 975-80.
200. Lincoln RA, Vorhees DJ, Chesney EJ, Shine JP, Grandjean P, Senn DB. Fish consumption and mercury exposure among Louisiana recreational anglers. Environ Health Perspect 2011; 119: 245-51.

201. Yorifuji T, Tsuda T, Grandjean P. Unusual cancer excess after neonatal arsenic exposure from contaminated milk powder. J Natl Cancer Inst 2010; 102: 360-1.
202. Harari R, Julvez J, Murata K, Barr D, Bellinger DC, Debes F, Grandjean P. Neurobehavioral deficits and increased blood pressure in school-age children prenatally exposed to pesticides. Environ Health Perspect 2010; 118: 890-6.
203. Grandjean P, Satoh H, Murata K, Eto K. Adverse effects of methylmercury: Environmental health research implications. Environ Health Perspect 2010; 118: 1137-45.
204. Mahaffey KR, Sunderland EM, Chan HM, Choi AL, Grandjean P, Mariën K, Oken E, Sakamoto M, Schoeny R, Weihe P, Yan C-H, Yasutake A. Balancing the benefits of n-3 polyunsaturated fatty acids and the risks of methylmercury exposure from fish consumption. Nutrit Rev 2011; 69: 493-508.
205. Julvez J, Debes F, Weihe P, Choi A, Grandjean P. Sensitivity of continuous performance test (CPT) to mercury exposure at age 14 years. Neurotoxicol Teratol 2010; 32: 627–32.
206. Dalgård C, Petersen MS, Schmedes AV, Brandslund I, Weihe P, Grandjean P. High latitude and marine diet: Vitamin D status in elderly Faroese. Br J Nutr 2010; 104: 914-8.
207. Heilmann C, Budtz-Jørgensen E, Nielsen F, Heinzow B, Weihe P, Grandjean P. Serum concentrations of antibodies against vaccine toxoids in children exposed perinatally to immunotoxicants. Environ Health Perspect 2010; 118: 1434-8.
208. Grandjean P, Poulsen LK, Heilmann C, Steuerwald U, Weihe P. Allergy and sensitization during childhood associated with prenatal and lactational exposure to marine pollutants. Environ Health Perspect 2010; 118: 1429-33.
209. Grandjean P, Henriksen JE, Choi AL, Petersen MS, Dalgård C, Nielsen F, Weihe P. Marine food pollutants as a risk factor for hypoinsulinemia and type 2 diabetes. Epidemiology 2011; 22: 410-7.
210. Yorifuji T, Debes F, Weihe P, Grandjean P. Prenatal exposure to lead and cognitive deficit in 7- and 14-year-old children in the presence of concomitant exposure to similar molar concentration of methylmercury. Neurotoxicol Teratol 2011; 33: 205-11.
211. Grandjean P. Even low-dose lead exposure is hazardous. The Lancet 2010; 375: 855-6.
212. Spulber S, Rantamäki T, Nikkilä O, Castrén E, Weihe P, Grandjean P, Ceccatelli S. Effects of maternal smoking and exposure to methylmercury on Brain-Derived Neurotrophic Factor (BDNF) concentrations in cord serum. Toxicol Sci 2010; 117: 263–9.
213. Mozaffarian D, Shi P, Morris JS, Spiegelman D, Grandjean P, Siscovick, Willett WC, Rimm EB. Mercury exposure and risk of cardiovascular disease in two U.S. cohorts. N Engl J Med 2011; 364: 1116-25.
214. Ozonoff DM, Grandjean P. Milestones and impact factors (editorial). Environ Health 2010; 9: 35.
215. Needham LL, Grandjean P, Heinzow B, Jørgensen PJ, Nielsen F, Patterson DG Jr, Sjödin A, Turner WE, Weihe P. Partition of environmental chemicals between maternal and fetal blood and tissues. Environ Sci Technol 2011; 45: 1121-6.
216. Yorifuji T, Grandjean P, Tsuda T, Kashima S, Doi H. Cancer excess after arsenic exposure from contaminated milk powder. Environ Health Prev Med 2011; 16: 164-70.
217. Grandjean P, Herz K. Methylmercury and brain development: Imprecision and underestimation of developmental neurotoxicity in humans. Mt Sinai J Med 2011: 78: 107-18.
218. Pichery C, Bellanger M, Zmirou-Navier D, Glorennec P, Hartemann P, Grandjean P. Childhood lead exposure in France: benefit estimation and partial cost-benefit analysis of lead hazard control. Environ Health 2011; 10: 44.

219. Wohlfahrt-Veje C, Main KM, Schmidt IM, Boas M, Jensen TK, Grandjean P, Skakkebæk NE, Andersen HR. Lower birth weight and increased body fat at school age in children prenatally exposed to modern pesticides: A prospective study. Environ Health 2011; 10: 79.
220. Wohlfahrt-Veje C, Andersen HR, Schmidt IM, Aksglaede L, Sørensen K, Juul A, Jensen TK, Grandjean P, Skakkebæk NE, Main KM. Early Breast Development in Girls after Prenatal Exposure to Non-Persistent Pesticides. Int J Androl 2012; 35: 273-82.
221. Dalgård C, Petersen MS, Weihe P, Grandjean P. Vitamin D status in relation to type 2 diabetes development. Diabetes Care 2011; 34: 1284-8.
222. Julvez J, Debes F, Weihe P, Choi AL, Grandjean P. Thyroid dysfunction as a mediator of organochlorine neurotoxicity in preschool children. Environ Health Perspect 2011; 119:1429-35.
223. Audouze K, Grandjean P. Application of computational systems biology to explore environmental toxicity hazards. Environ Health Perspect 2011; 119: 1754-9.
224. Grandjean P, Andersen EW, Budtz-Jørgensen E, Nielsen F, Mølbak K, Weihe P, Heilmann C. Decreased serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA 2012; 307: 391-7.
225. Grandjean P, Eriksen ML, Ellegaard O, Wallin JA. The Matthew effect in environmental science publication: A bibliometric analysis of chemical substances in journal articles. Environ Health 2011; 10: 96.
226. Vestergaard S, Nielsen F, Andersson AM, Hjøllund NH, Grandjean P, Andersen HR, Jensen TK. Association between perfluorinated compounds and time to pregnancy in a prospective cohort of Danish couples attempting to conceive. Human Reproduct 2012; 27: 873-80.
227. Wohlfahrt-Veje C, Andersen HR, Jensen TK, Grandjean P, Skakkebaek NE, Main KM. Smaller genitals at school age in boys whose mothers were exposed to non-persistent pesticides in early pregnancy. Int J Androl 2012; 35: 265-72.
228. Grandjean P, Weihe P, Nielsen F, Heinzow B, Debes F, Budtz-Jørgensen E. Neurobehavioral deficits at age 7 years associated with prenatal exposure to toxicants from maternal seafood diet. Neurotoxicol Teratol 2012; 34: 466-72.
229. Grandjean P, Grønlund C, Kjær IM, Jensen TK, Sørensen N, Andersson AM, Juul A, Skakkebæk NE, Budtz-Jørgensen E, Weihe P. Reproductive hormone profile and pubertal development in 14-year-old boys prenatally exposed to polychlorinated biphenyls. Reprod Toxicol 2012; 34: 498-503.
230. Karagas MR, Choi AL, Oken E, Horvat M, Schoeny R, Kamai E, Grandjean P, Korrick S. Evidence on the human health effects of low level methylmercury exposure. Environ Health Perspect 2012; 120: 799-806.
231. Grandjean P, Ozonoff D. Portrait of the journal as a young adult. Environ Health. 2012; 11: 30.
232. Budtz-Jørgensen E, Bellinger D, Lanphear B, Grandjean P, International Pooled Lead Study Investigators. An international pooled analysis for obtaining a benchmark dose for environmental lead exposure in children. Risk Anal 2013; 33: 450-61.
233. Færch K, Højlund K, Vind BF, Vaag A, Dalgård C, Nielsen F, Grandjean P. Increased serum concentrations of persistent organic pollutants among prediabetic individuals: potential role of altered substrate oxidation patterns. J Clin Endocrinol Metab 2012; 97: E1705-13.
234. Yorifuji T, Murata K, Bjerve K, Choi AL, Weihe P, Grandjean P. Visual evoked potentials in children prenatally exposed to methylmercury. Neurotoxicology 2013; 37: 15-8.
235. Pichery C, Bellanger M, Zmirou-Navier D, Fréry N, Cordier S, Roue-LeGall A, Hartemann

P, Grandjean P. Economic evaluation of health consequences of prenatal methylmercury exposure in France. Environ Health 2012; 11: 53.
236. Andersen HR, Wohlfahrt-Veje C, Dalgård C, Christiansen L, Main KM, Christine Nellemann C, Murata K, Jensen TK, Skakkebæk NE, Grandjean P. Paraoxonase 1 polymorphism and prenatal pesticide exposure associated with adverse cardiovascular risk profiles at school age. PLoS ONE 2012; 7(5): e36830.
237. Choi AL, Sun G, Zhang Y, Grandjean P. Developmental fluoride neurotoxicity: A systematic review and meta-analysis. Environ Health Perspect 2012; 120: 1362-8.
238. Mozaffarian D, Shi P, Morris JS, Grandjean P, Siscovick D, Spiegelman D, Willett W, Rimm E, Curhan G, Forman J. Mercury exposure and risk of hypertension in US men and women in two prospective cohorts. Hypertension 2012; 60: 645-52.
239. Wu H, Bertrand KA, Choi AL, Hu FB, Laden F, Grandjean P, Sun Q. Plasma levels of persistent organic pollutants and risk of type 2 diabetes: a prospective analysis in the Nurses' Health Study and meta-analysis. Environ Health Perspect 2013; 121: 153-61.
240. Barouki B, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable diseases and dysfunctions: Implications for research and public health. Environmental Health 2012: 11: 42.
241. Julvez J, Davey-Smith G, Golding J, Ring S, St. Pourcain B, Gonzalez JR, Grandjean P. Prenatal methylmercury exposure and genetic predisposition to cognitive deficit at age 8 years. Epidemiology 2013; 24: 643-50.
242. Balbus JM, Barouki R, Birnbaum LS, Etzel RA, Gluckman PD, Grandjean P, Hancock C, Hanson MA, Heindel JJ, Hoffman K, Jensen GK, Keeling A, Neira M, Rabadán-Diehl C, Ralston J, Tang KC. Early-life prevention of non-communicable diseases (Comment). Lancet 2013; 381: 3-4.
243. Dietz R, Sonne C, Basu N, Braune B, O'Hara T, Letcher RJ, Scheuhammer T, Andersen M, Andreasen C, Andriashek D, Asmund G, Aubail A, Baagøe H, Born EW, Chan HM, Derocher AE, Grandjean P, Knott K, Kirkegaard M, Krey A, Lunn N, Messier F, Obbard M, Olsen MT, Ostertag S, Peacock E, Renzoni A, Rigét FF, Skaare JU, Stern G, Stirling I, Taylor M, Wiig O, Wilson S, Aars J. What are the toxicological effects of mercury in Arctic biota? Sci Total Environ 2013; 443: 775-790.
244. Bellanger M, Pichery C, Aerts D, Berglund M, Castaño A, Čejchanová M, Crettaz P, Davidson F, Esteban M, Fischer ME, Gurzau AE, Halzlova K, Katsonouri A, Knudsen LE, Kolossa-Gehring M, Koppen G, Ligocka D, Miklavčič A, Reis MF, Rudnai P, Tratnik JS, Weihe P, Budtz-Jørgensen E, Grandjean P. Economic benefits of methylmercury exposure control in Europe: Monetary value of neurotoxicity prevention. Environ Health 2013; 12: 3.
245. Halling J, Petersen MS, Jørgensen N, Jensen TK, Grandjean P, Weihe P. Semen quality and reproductive hormones in Faroese men – a cross-sectional population-based study of 481 men. BMJ Open 2013; 3: e001946.
246. Grandjean P, Budtz-Jørgensen E. Immunotoxicity of perfluorinated alkylates: Calculation of benchmark doses based on serum concentrations in children. Environ Health 2013; 12: 35.
247. Choi AL, Mogensen UB, Bjerve K, Weihe P, Grandjean P, Budtz-Jørgensen E. Negative confounding by essential fatty acids in methylmercury neurotoxicity associations. Neurotoxicol Teratol 2014; 42: 85-92.
248. Mozaffarian D, Shi P, Morris JS, Grandjean P, Siscovick DS, Spiegelman D, Hu FB. Methylmercury exposure and incident diabetes mellitus in US men and women in two prospective cohorts. Diabetes Care 2013; 36: 3578-84.

249. Audouze K, Brunak S, Grandjean P. Computational approach to chemical etiologies of diabetes. Sci Comm 2013; 3: 2712.
250. Fonseca MF, Hacon SS, Grandjean P, Choi AL, Bastos WR. Iron status as a covariate in methylmercury-associated neurotoxicity risk. Chemosphere 2014; 100: 89-96.
251. Grandjean P, Clapp R. Changing interpretation of human health risks from perfluorinated compounds. Publ Health Rep 2014:129; 482-5.
252. Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. Lancet Neurol 2014; 13: 330-8.
253. Kim BM, Choi A, Ha EH, Pedersen L, Nielsen F, Weihe P, Hong YC, Budtz-Jørgensen E, Grandjean P. Effect of hemoglobin and selenium on partition of mercury between maternal and cord blood. Environ Res 2014; 132: 407-12.
254. Grandjean P, Ozonoff D. Transparency and translation of science in a modern world. Environ Health 2013; 12: 70.
255. Tang-Peronard JL, Heitmann BL, Andersen HR, Steuerwald U, Grandjean P, Weihe P, Jensen TK. Association between prenatal polychlorinated biphenyl exposure and obesity development at ages 5 and 7 y: a prospective cohort study of 656 children from the Faroe Islands. Am J Clin Nutrit 2014; 99: 5-13
256. Timmermann CAG, Rossing LI, Grøntved A, Ried-Larsen M, Dalgård C, Andersen LB, Grandjean P, Nielsen F, Svendsen KD, Scheike T, Jensen TK. Adiposity and glycemic control in children exposed to perfluorinated compounds. J Clin Endocrinol Metab 2014; 99: E608-14.
257. Julvez J, Grandjean P. Genetic susceptibility to methylmercury developmental neurotoxicity matters. Front Genet 2013; 4: 278.
258. Vesterholm Jensen D, Christensen JH, Virtanen HE, Skakkebæk NE, Main KM, Toppari J, Veje CV, Andersson AM, Nielsen F, Grandjean P, Jensen TK. No association between exposure to perfluorinated compounds and congenital cryptorchidism: a nested case-control study among 215 boys from Denmark and Finland. Reproduction 2014; 147: 411-7.
259. Li M, Sherman LS, Blum JD, Grandjean P, Mikkelsen B, Weihe P, Sunderland EM, Shine JP. Assessing sources of human methylmercury exposure using stable mercury isotopes. Environ Sci Technol 2014; 48: 8800-6.
260. Grandjean P, Herz KT. Trace elements as paradigms of developmental neurotoxicants. J Trace Elem Med Biol 2015; 31: 130-4.
261. Grandjean P, Weihe P, Debes F, Choi AL, Budtz-Jørgensen E. Neurotoxicity from prenatal and postnatal exposure to methylmercury. Neurotoxicol Teratol 2014; 43: 39-44.
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